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STATE OF THE ART PAPER ON SARCOIDOSIS

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None.

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ABSTRACT

Sarcoidosis is a systemic disease of unknown aetiology, characterised by non-caseating granulomatous inflammation. It most commonly manifests in the lungs and intra-thoracic lymph nodes but can affect almost any other organ. Our knowledge of the aetiology and immunopathogenesis of sarcoidosis remains incomplete. The enigma of sarcoidosis lies in its immunological paradox of Type 1 T helper cell (T_H1) dominated local inflammation coexisting with T regulatory (T_{reg}) induced peripheral anergy. Although specific aetiological agents have not been conclusively identified, there is increasing evidence suggesting environmental and microbial antigens may trigger sarcoid granulomatous inflammation. Genome-wide association studies have identified various candidate genes for sarcoid susceptibility and gene expression analyses have provided insights into the cytokine dysregulation which results. Sarcoidosis remains a diagnosis of exclusion based on histological evidence of non-caseating granulomas with compatible clinical and radiological findings. In recent years, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) of mediastinal lymph nodes has facilitated the diagnosis, and positron emission tomography (PET) scanning has improved localisation of occult disease sites throughout the body. There is no single biomarker that is adequately sensitive and specific for detecting and monitoring disease activity. Asymptomatic patients do not require treatment but when treatment is indicated, corticosteroids remain the initial standard of care, despite their adverse effect profile and immunosuppressive drugs are useful for long-term treatment. The tumour necrosis factor alpha (TNF-α) inhibitors have recently been studied as a treatment option for patients with refractory disease. This state of the art review will provide an updated and comprehensive review of our current understanding and highlight the need for further research into the immunopathogenesis and treatment of sarcoidosis.

SUMMARY STATEMENT

Sarcoidosis remains a disease of unknown aetiology, characterised by granuloma formation and it affects the lung in most cases. There are few long-term clinical trials to guide investigations, monitoring or treatment.

The diagnosis is best made based on the clinical presentation and supportive evidence, which can include characteristic chest CT findings, a peripheral blood lymphopenia, elevation of the angiotensin converting enzyme (ACE) level, hypercalcaemia and hypercalciuria. A confirmatory test would include a biopsy with non-caseating granulomas in the absence of another reason for granuloma formation. Endobronchial ultrasound (EBUS) is transforming the investigation of mediastinal nodes due to sarcoidosis and positron emission spectroscopy (PET) is gradually replacing the gallium scan for imaging and identifying areas of active disease.

There are few guides to indicate prognosis, but Löfgren's syndrome generally suggests a better outcome. The outlook for most patients with sarcoidosis is favourable with the majority achieving remission.

Monitoring of those with lung parenchymal disease is recommended for 5 years after the last indication of progression and that will usually include measurement of lung function and blood tests for liver dysfunction and hypercalcaemia as appropriate. The serum ACE level is used by some to indicate whether the disease remains active.

It is essential that all patients with pulmonary disease are also monitored for extrapulmonary manifestations; ophthalmologically on a regular basis, at least annually or more frequently if active disease and electrocardiography for conduction abnormalities and evidence of cardiac sarcoidosis, which remains rare, but important to recognise.

Treatment comprises symptomatic measures if necessary and a period of observation if possible before considering corticosteroids and/or immunosuppression. Most respiratory physicians will use corticosteroids and there is some limited evidence to support their use. There are few data supporting the use of immunosuppression but azathioprine, methotrexate and mycophenolate have been used. More recently, there is some limited evidence that biological agents, such as TNF-α inhibitors, may be beneficial.

The future will require well - funded multicentre trials to establish the appropriate place of the currently used agents as well as novel biological agents.

INTRODUCTION

The management of sarcoidosis remains a challenge despite new insights into its pathogenesis, the application of newer imaging techniques and diagnostic procedures and the use of biological agents for treatment. Some of the management difficulties that remain include: why the disease persists in a minority of patients, who requires treatment, which treatment to use, how to best monitor disease activity, how extensively to pursue a diagnosis and how to recognise cardiac involvement. This State of the Art will give a detailed review of recent advances in understanding the pathogenesis, diagnosis and management.

Sarcoidosis is a systemic granulomatous disease of unknown aetiology that primarily affects the lungs and lymphatic systems of the body, although any organ may be affected. Sarcoidosis is typically a diagnosis of exclusion, best supported by compatible clinical and radiological findings and/or demonstration of non-caseating granulomas in one or more systems with exclusion of other disorders known to cause granulomatous disease. The disease spectrum may range from asymptomatic patients to those with severe organ dysfunction. Most patients do not require treatment although, when necessary, patients usually improve initially with moderate doses of corticosteroids. There have been few randomised controlled studies to guide appropriate treatment, despite the progress in understanding the immunopathological and genetic features of the disorder. During the past decade and since the 1999 combined American Thoracic Society (ATS), European Respiratory Society (ERS) and World Association of Sarcoidosis and Other Granulomatous Diseases (WASOG) Statement on Sarcoidosis (1), there have been significant advances in the study of sarcoidosis; however, a great deal remains to be discovered.

DEFINITION AND PURPOSE

The primary purpose of this TSANZ State of the Art Paper is to provide an update on sarcoidosis because more than 7000 relevant papers have been published since the 1999 ATS/ERS/WASOG Statement on Sarcoidosis. This paper aims to expand on the ATS/ERS/WASOG statement and to provide a comprehensive summary of the current literature regarding sarcoidosis, including the immunopathogenesis, aetiology and genetic factors, as well as the challenges of diagnosis and treatment. It is hoped that this paper will improve patient care, as well as stimulate new research to further investigate the aetiology, pathogenesis, disease biomarkers and treatment of sarcoidosis.

HISTORY OF SARCOIDOSIS

Sarcoidosis was first described in 1877 by Jonathan Hutchinson in a patient with non-tender purple peripheral cutaneous plaques (1–3). Hutchinson described these lesions as a “livid papillary psoriasis” in additional cases (4) and attributed them to a manifestation of gout (5). . Carl Boeck published illustrations of sarcoid skin lesions (2). He termed these lesions “multiple benign sarkoid of the skin” and noted epithelioid and giant cells on histological examination (6). He coined the term “sarkoid”, derived from the Greek for “sark” and “oid” meaning “fleshy condition” (7). Caesar Boeck (his nephew) described 24 cases of “benign miliary lupoids”, also involving the lungs, conjunctiva, bone, lymph nodes, spleen and nasal mucosa which identified the condition as a multisystem disease (2). In 1889, Besnier described lupus pernio (8) and the histological features were characterised three years later by Tenneson (9).

Christian Heerfordt described ‘uveo-parotid fever’ characterised by a chronic, febrile course with parotid gland enlargement, uveitis as well as cranial nerve palsies, especially involving the facial nerve with cerebrospinal fluid pleocytosis (10), now a recognised form of sarcoidosis. Jörgen Shaumann (1879–1953) identified patients with multi-organ involvement, including bone, lung, tonsils, gums, spleen and liver (11). Schaumann hypothesised this was a systemic disorder, which he termed “lymphogranulomatose benigna” to distinguish it from Hodgkin’s malignant granuloma (12) and believed that sarcoidosis represented a variant of tuberculosis (1). Sven Löfgren (1910–1978) described a syndrome that occurs at the onset in some Caucasians, characterised by erythema nodosum, bilateral hilar lymphadenopathy, fever and polyarthritis

(13), since termed Löfgren's syndrome. Autopsy studies and large clinical series further identified the natural history and clinical features of sarcoidosis (14–21).

Ansgar Kveim, (1941), noted that an intradermal injection of sarcoid lymph node tissue elicited a papular eruption in 12 of 13 patients with sarcoidosis. He concluded that this was caused by an unknown agent, distinct from tuberculosis (22). Louis Siltzbach modified this injection using a suspension derived from sarcoid spleen and affirmed its specificity in an international study (23), becoming known as the Kveim-Siltzbach test, which was used as a diagnostic test but with concerns regarding human tissue, is no longer used routinely in clinical practice (24).

Corticosteroids were initially used to treat sarcoidosis in 1951, with several small studies indicating favourable responses in subsets of patients (15, 25–29). However, corticosteroid efficacy was difficult to evaluate in patients with spontaneous remission, especially in those with early disease, e.g. Löfgren's syndrome or bilateral hilar lymphadenopathy on chest radiographs (15, 17–19). Radiographic staging classification systems were proposed to characterise the various pulmonary manifestations of sarcoidosis and were used as a guide for classification (15, 30). The role of corticosteroids was evaluated in several prospective, randomised trials comparing patients stratified based on pulmonary radiological staging classifications (31–35). These studies only demonstrated a modest role for corticosteroids in modifying the disease, but nevertheless indicated the heterogeneous nature and clinical course of sarcoidosis, which means that subgroups of patients needed to be selected and clinical trials adequately powered (1). During the mid-1970s, the availability of computed tomography and fibreoptic bronchoscopy facilitated the diagnosis of sarcoidosis with reduced morbidity and higher sensitivity (1, 36). Retrieval of leukocytes via bronchoalveolar lavage (BAL) during bronchoscopy, along with flow cytometric laboratory techniques, greatly contributed to the understanding of the immunopathogenesis of sarcoidosis (37, 38) and such studies continue to provide new insights into sarcoidosis (24).

Geraint James and others formed the International Committee on Sarcoidosis to develop a research base for studies on sarcoidosis, later replaced by the World Association of Sarcoidosis and Other Granulomatous Conditions (WASOG) (2, 39). In 1975 the serum ACE level was first recognised as a possible biomarker for active disease (38, 40).

There have been major advances in our understanding of sarcoidosis since WASOG was founded, with many informative genetic, immunological, environmental and therapeutic studies. There is now a greater understanding of the cytokine network involved in granuloma formation as well as the role of different genotypes in predisposing to the various clinical phenotypes of sarcoidosis. This has led to an ongoing effort to identify the aetiology of the disease, with investigation of various antigenic proteins.

EPIDEMIOLOGY

Racial, demographic and ethnic variations in clinical manifestations of sarcoidosis clearly exist. Sarcoidosis affects people of all ages regardless of race and ethnicity, with a peak incidence among people aged 20 to 39 years old (41, 42). While the incidence of sarcoidosis varies worldwide, the highest incidence is observed in northern European countries at 5–40 cases per 100,000 people (43). Sarcoidosis has recently emerged as the most common cause of interstitial lung disease in many Western countries (44, 45). Finland has a reported incidence of 28.2 cases per 100,000 people, which is much higher than that in Japan at 3.7 per 100,000 (46, 47). African-Americans have a peak incidence in the fourth decade of life (48) and the annual incidence is threefold that of Caucasian Americans (35.5 per 100,000 compared to 10.9 per 100,000) (41). African-Americans have a lifetime risk of 2.4% compared to 0.85% of Caucasian Americans (49) and Afro-Caribbeans contributed to 66% of cases in the United States. African-Americans are also more likely to suffer from more chronic and fatal disease phenotypes (50). In other countries, the prevalence is estimated at 4.4–6.3 per 100,000 in Australia (51, 52), 20 per 100,000 in the United Kingdom, 64 per 100,000 in Sweden, 10 per 100,000 in France, 9 per 100,000 in Germany, 1.4 per 100,000 in Spain and 7 per 100,000 in Greece (53).

In regards to age of onset, only 18% of patients in Greece presented between 20–40 years old compared to 96% in the UK. Asians and Africans are more likely to present with extra-thoracic disease, which is more severe and extensive than those seen in Caucasians (54). Löfgren's syndrome, affects 28% of patients in the UK but is almost unheard of in Japan (55). Up to half of the patients with sarcoidosis in Japan have uveitis, but only 5% has been reported in Denmark (46).

Some studies reported an overall predominance of sarcoidosis among females compared to males, while others revealed no gender predilection (19, 41, 56, 57). Women made up 41% of cases in India compared to 71% in Greece. In Sweden, women have a 1.3 times higher risk of sarcoidosis than men (21). Females were found to have more ocular and neurological involvement, compared to men who had a higher risk of hypercalcaemia (46).

Occupational exposures to certain chemicals and specific geographical locations are thought to contribute to an increased risk of sarcoidosis. The ACCESS study in the USA gathered data from 10 specialist centres across the country and found an association between sarcoidosis and agricultural employment, including exposure to microbial aerosols or insecticides (58). Other suggested occupational triggers included exposure to titanium, vegetable dust and photocopier toner (59). Löfgren's syndrome has been reported to have a peak prevalence during the spring season, further suggesting an environmental trigger for the disease (60).

Socio-economic status does not appear to influence the risk of sarcoidosis, although financial barriers and poor access to healthcare have been associated with a more serious condition at initial presentation (61). This may be a consequence of under-diagnosing sarcoidosis at an early stage (53, 62), inadequately sensitive and specific diagnostic tests and a variation in disease presentation. Likewise case ascertainment differences may account for some of the variation seen between these studies, and it would be helpful to have an international study using the same ascertainment method.

ADVANCES IN THE AETIOLOGY AND PATHOGENESIS OF SARCOIDOSIS

The aetiology of sarcoidosis remains unclear although there is an improved understanding of the genetic factors involved, the environmental associations, the putative antigens and its immunopathogenesis. There are different lines of evidence suggesting that sarcoidosis results from exposure of genetically susceptible individuals to specific, different, environmental agents. This is supported in part by several epidemiological studies including ACCESS (58, 63–74). The type of inflammatory response in sarcoidosis may be interpreted as a reaction to foreign stimuli and is characterised by foci of large numbers of activated macrophages and CD4 T lymphocytes at disease sites (24, 37, 75). There is a pattern of cytokine production that is predominantly a T_H1 type immune response (76–83), with T_H17 features also implicated (84–86). This pattern is triggered by a limited number of antigens (3), as indicated by studies investigating T cell receptor (TCR) phenotypes in patients with sarcoidosis (87–92).

1) Genetic Factors and Genome-Wide Association Studies

Familial clustering of disease, increased concordance in monozygotic twins and racial differences in disease incidence suggest that genetic factors play a role in the pathogenesis of sarcoidosis, as well as clinical presentation and outcomes (24, 93, 94). Despite the low population incidence of sarcoidosis, familial clustering of sarcoidosis cases has been observed worldwide and occurs in approximately 5–16% of patients (69, 95–99). ACCESS evaluated 706 patients with sarcoidosis with matched controls and found a five-fold risk of having siblings or parents with sarcoidosis (odds ratio for siblings 5.8, 95% CI 2.1–15.9) and an increased risk in first- and second-degree relatives. Additionally, a Danish and Finnish population-based registry twin study identified an 80-fold increased risk in monozygotic twins compared to a 7-fold risk in dizygotic twins (100). As noted above, variations exist between different racial groups worldwide (94, 101).

Through a classical candidate gene approach, several genes of importance have been identified in sarcoidosis, although more recently Genome Wide Association Studies (GWAS) have been utilised, which have identified new genetic associations with sarcoidosis (102). Consistent associations are seen with specific human leukocyte antigen (HLA) alleles across different ethnic populations (102–104) and a polymorphism in the butyrophilin-like 2 receptor (*BTNL2*) gene, conferring disease susceptibility (105). Genetic associations may relate to differences in antigenic processing and presentation by antigen presenting cells, and to the control of cytokine release, and these variations could affect the prognosis and clinical manifestations of sarcoidosis (106). Nonetheless, there appears to be no unifying genetic "signature" of sarcoidosis,

but associations with certain disease subtypes or within populations exist, indicating that susceptibility to sarcoidosis is complex and polygenic in nature (102, 107).

The HLA Class I general susceptibility alleles which are consistently associated with acute sarcoidosis risk include HLA-A*1, HLA-B*7 and HLA-B*8 (108–111). HLA-B*8/HLA-DR3 haplotype is uniquely associated with susceptibility in Caucasians, suggesting that HLA Class I genes may simply be related to linkage disequilibrium with Class II genes (102), although HLA-B*7 and B*8 appear to increase the risk of sarcoidosis independently of Class II alleles (112).

The suspected immunopathogenesis of sarcoidosis involves the presentation of a limited class of insoluble antigens, expressed on HLA Class II molecules on the surface of antigen-presenting cells, which activates CD4+ lymphocytes and triggers a granulomatous immune response. HLA Class II genes are therefore likely to play a significant role in sarcoidosis susceptibility (102). Table 1 summarises the key HLA gene associations identified in sarcoidosis. Class II HLA-DRB1 genes affect both susceptibility and prognosis. HLA-DRB1 and HLA-DQB1 alleles have been consistently associated with African-Americans (AA) and Caucasians (C) who develop Löfgren's syndrome, and an ~80% rate of spontaneous remission (113–116). HLA-DQB1*0201 and HLA-DRB1*0301 are also associated with Löfgren's syndrome, with reduced T_H1 responses and cytokine expression (117–121). In ACCESS, the HLA-DRB1*1101 allele was significantly associated with sarcoidosis in both AA and C populations, with an attributable risk of 16% and 9% respectively (66). There have also been phenotypic variations, with HLA-DRB1*0401 being associated with ocular sarcoid in both groups and DRB3 with bone marrow involvement (66).

T cells from sites of sarcoid disease activity, including from Kveim-Siltzbach skin reactions, also show a restricted variable-α region (Vα) and Vβ region of the T cell receptor (TCR), indicating TCR oligoclonal expansion in response to a limited group of antigens (87–89, 91). BAL T cells from HLA-DRB1*0301 positive patients with sarcoidosis predominantly express Vα2.3 (AV2S3+), which indicates that these T cells are reacting to the unknown sarcoid antigen(s) when presented by the HLA-DRB1*0301 molecule (122–124). However, unlike αβ+ T cells, there is generally no increase in γδ+ T cell receptor expressing lymphocytes in patients with sarcoidosis, the γδ+ receptor being postulated to be part of a defence mechanisms against intracellular pathogens, e.g. mycobacteria (125).

Chronic and severe pulmonary sarcoidosis has been consistently associated with the HLA-DRB1*1501/HLA-DQB1*0602 haplotype (121, 126, 127). A recent study of 754 patients identified distinct differences in distribution of HLA alleles in Löfgren's and non-Löfgren's syndrome patients, indicating that persistent disease is also associated with DRB1*07, DRB1*14 and DRB1*15 (120). There is also an association between sarcoidosis susceptibility and a *BTNL2* gene single nucleotide polymorphism (rs2076530 G->A), independent of HLA Class II alleles, which affects T lymphocyte activation and regulation (128). The *BTNL2* gene was first linked to sarcoidosis when a GWAS from 63 German families identified a linkage to chromosome 6p21 (129) and subsequent scanning of the MHC region identified this sarcoidosis risk variant (130). The *BTNL2* gene resides in the HLA Class II region of chromosome 6p, a B7 family T-cell negative co-stimulatory molecule, related to the CD80 and CD86 co-stimulatory receptors (128, 130, 131). Theoretically, a non-functional BTNL2 molecule could result in exaggerated lymphocyte activation (132), consistent with the pathogenesis of sarcoidosis.

Studies linking sarcoidosis with non-HLA candidate genes have been inconsistent, with genes encoding tumour-necrosis factor-α (TNF-α) and chemokine receptors being logical candidates, but most do not display significant associations with sarcoidosis (106, 107, 133, 134). Some studies indicate interferon (IFN) gene polymorphisms are associated with sarcoidosis susceptibility (135) and a haplotype of the C-C chemokine receptor 2 (CCR2) gene with Löfgren's syndrome independent of HLA-DRB1*0301 (136). Table 2 summarises some other important non-HLA genes reported in association with sarcoidosis.

Toll-like receptors (TLR) are a group of transmembrane receptors expressed on the surface of antigen-presenting cells that are activated by pathogen-associated molecular patterns (137, 138). TLR4 gene polymorphisms may regulate the innate immune response in sarcoidosis (139) and have been shown to be associated with a chronic course in sarcoidosis (140). Serum amyloid-A, an amyloid precursor protein and innate receptor ligand (141), has similar physicochemical properties to sarcoidosis tissue extracts (142). It is extensively deposited in sarcoid granulomas and it is capable of eliciting T_H1 immune responses through TLR2 in an experimental model of sarcoidosis, and it may be a potential biomarker (143–145). In addition, TLR and innate immune responses may contribute to granuloma formation (146, 147).

A recent GWAS of 499 German patients with sarcoidosis and 490 control subjects identified a series of genetic associations with sarcoidosis. The strongest signal mapped to the annexin A11 (ANXA11) gene on chromosome 10q22.3, with this association being confirmed by validation in an independent sample (148) of 1689 cases of sarcoidosis (149). Annexin A11 has important functions in the regulation of calcium signalling, cell division, vesicle trafficking and cell apoptosis and may affect the apoptosis pathway in sarcoidosis (148). An important aspect of genome-wide scanning studies, however, is the requirement for adequate fine-mapping and functional studies after the initial scan to identify the biological relevance of the initial findings (150) and most studies are under-powered.

2) Role of Environmental Factors and ACCESS

Since sarcoidosis most commonly affects the lungs, intrathoracic lymph nodes, skin and eyes, the search for environmental causes has focussed mainly on exposure to airborne antigens. Spatial clustering of unrelated cases of sarcoidosis suggested that exposure to common environmental agent(s) can trigger the development of sarcoidosis. The earliest studies on environmental risk factors reported associations with wood-burning stoves, pine pollen and living in rural areas (51, 151). Inorganic particles (59), mouldy environments (63, 152), high indoor humidity, insecticides, peanut dust, pica and exposures to synthetic mineral fibres are also associated (63, 116). Beryllium, titanium, aluminium, zirconium, chromium, nickel and talc exposure can also induce sarcoid-like granuloma formation (116, 153). Berylliosis resembles sarcoidosis, but has different genetic susceptibilities and is identified by history and a positive beryllium lymphocyte proliferation test (154–156).

Occupational studies have also shown positive disease associations with service in the U.S. Navy (157), metalworking (152), fire-fighting (158) and the handling of building supplies (159). There has also been an increased incidence of sarcoidosis among New York City Fire Department rescue workers, maintenance workers, healthcare workers and police officers involved in the 2001 World Trade Centre disaster, possibly related to the dust burden exposure (160, 161). There is also a seasonal influence, with erythema nodosum present most commonly in the winter and early spring months, in both the northern and southern hemispheres (162, 163). Immune dysregulation following allogeneic haematopoietic cell transplantation has also been shown to promote sarcoidosis in patients with susceptible HLA genotypes (164). Individuals have also been reported to develop granulomatous inflammation following lung and heart transplantation from donors with sarcoidosis (165–167). The Kveim-Siltzbach test could support the concept of a transmissible agent (168). Tobacco smoking (active, passive and past) has been associated with a reduced risk of sarcoidosis, probably related to smoking deactivating the M2 alveolar macrophage phenotype as opposed to the classically activated M1 phenotype induced by the T_H1 response (169–172).

The ACCESS study identified several environmental exposures associated with increased disease risk including insecticides, pesticides, agricultural employment and microbial bioaerosols (mould and/or mildew, musty odours). These were associated with a 1.5 increase in the risk of sarcoidosis. There was also a reduced risk associated with exposures to animal dander and other allergic T_H2 responses (63, 65). The ACCESS study, however, did not have adequate power to ascertain sarcoidosis risk amongst fire rescue workers, military personnel and healthcare workers. In addition, it did not prove an association with previously hypothesised exposures (e.g. wood dust, metals and silica) (173). The authors concluded that these results reflect exposure to microbial-rich environments and that a direct causal link between these factors and sarcoidosis was unlikely, suggesting multiple triggers exist. Even though there is support for including environmental agents as risk factors for sarcoidosis, the current evidence does not strongly favour a specific environmental or occupational exposure (63, 174).

3) Mycobacteria and other putative antigens

Diseases with similar clinical, pathological and immunological features as sarcoidosis, such as tuberculosis, chronic beryllium disease and hypersensitivity pneumonitis, illustrate that granulomatous diseases may or may not have an infectious aetiology (175). The microbiome has been invoked as an important potential player in this disease, but convincing replicated studies are awaited.

The inability to identify viable micro-organisms by direct histological staining and microbial culture methods from pathological tissues remains one of the strongest arguments against the role of infectious agents in the aetiology

of sarcoidosis. However, molecular analysis of sarcoidosis specimens suggests that mycobacteria and perhaps propionibacteria have a role in the pathogenesis of sarcoidosis, by the identification of microbial nucleic acids in sarcoid tissue specimens. With the use of special stains or culture methods some investigators have been able to identify micro-organisms in sarcoid tissues, most commonly those resembling mycobacteria (176, 177), as well as tuberculostearic acid (178) and muramyl dipeptide (179), both components of the mycobacterial cell wall, in sarcoid tissues. Schaumann bodies are a type of inclusion body found in sarcoid giant cells, which consist of small calcific deposits of calcium carbonate, iron and oxidised lipid with a lamellar morphology. They are identified in up to 88% of cases of sarcoidosis and arise from lysosomes (180). They have interestingly been identified as sites of mycobacterial degradation by demonstrating the localisation of lysosomal components and mycobacterial antigens in immunohistologically stained sarcoidosis tissue (181). Other investigators identified bacterial structures in skin and lymph node biopsies (182), as well as blood, bronchial washings, ocular anterior chamber fluid and cerebrospinal fluid from patients with sarcoidosis (183–187). These organisms were identified as 'L-form' cell-wall deficient bacteria, which can occur during the life-cycle of mycobacteria or in response to inhospitable conditions (176, 186, 188). However, in a larger multicentre study of 197 patients with sarcoidosis and 150 controls, an equal frequency of cell-wall deficient forms were observed in blood specimens (184). Sarcoidosis can also be histologically similar to lesions in atypical mycobacterial infections, including *Mycobacterium avium-intracellulare* complex (MAC), *Mycobacterium marinum* and following BCG vaccination (176, 187). Sarcoidosis is an important differential diagnosis of *M. marinum* infection, where the acid-fast bacilli are detected in 22% of active cases and the use of the polymerase chain reaction (PCR) is more useful for diagnosis (189, 190). Other organisms, including evidence of fungi within sarcoid tissues is case-based and does not explain the worldwide sarcoid distribution due to geographical limitations of most fungal species (116). Similarly, evidence linking *Rickettsia helvetica*, *Chlamydia pneumonia* and *Tropheryma whipplei* to sarcoidosis is weak, based on case reports and *Borrelia burgdorferi* DNA has not been detected in sarcoid tissues using PCR techniques (116, 174).

To improve the diagnostic sensitivity of traditional culture techniques, many investigators have used DNA amplification techniques to search for mycobacterial or propionibacterial infection in sarcoidosis. Investigations have used PCR and nested PCR techniques to identify mycobacterial and propionibacterial DNA or RNA in sarcoid tissue specimens, including fresh tissues, paraffin-embedded tissues, granulomas, lymph nodes, lung and BAL sediments and archival biopsy specimens. Several reports emerged indicating the presence of mycobacterial DNA in some sarcoid tissues using DNA primers for *M. tuberculosis* complex organisms, including mycobacterial 16S rRNA or RNA polymerase B in 60% of sarcoid granulomas and none in controls (191–196), which could also suggest cell wall deficient mycobacterial infection. However, other groups did not find fluorescent in situ hybridisation or PCR evidence of mycobacterial DNA or RNA in sarcoid tissues (197–199). A recent meta-analysis of 31 such studies identified that 231 out of 874 (26.4%) sarcoidosis biopsy specimens had evidence of mycobacterial DNA, which is 9- to 19-fold higher than control tissue samples, supporting an association between mycobacterial infection and sarcoidosis (200). It is important to note that these results are not reproducible in all patients and that treatment of sarcoidosis with corticosteroids is not associated with a reactivation of tuberculosis. These observations do not support a direct role of mycobacterial infection in sarcoidosis (201). In a patient with negative microscopy, culture and PCR for tuberculosis, the presence of compatible clinical features and histology allows a diagnosis of sarcoidosis to be made with confidence.

Based on hypotheses that pathogenic antigens in sarcoidosis have similar physicochemical properties as the Kveim-Siltzbach reagent (with poor solubility in neutral detergent and resistance to acidity and protease digestion) (142), this led to a limited proteomics approach to determine potential antigens with these characteristics in sarcoidosis tissue homogenates (202). Using mass spectroscopy and protein immunoblotting, mycobacterial catalase-peroxidase (KatG) peptides were later identified in 75% of samples, and were a target of circulating specific IgG in 48% of sarcoidosis subjects. In situ hybridisation localised KatG and 16S rRNA DNA to the inside of the sarcoid granulomas (202). This study was not based on any *a priori* hypothesis regarding specific microbes or auto-antigens and hence suggested that remnant mycobacterial proteins are a target of the adaptive cellular and humoral immune response driving granulomatous inflammation in at least a subset of sarcoid granulomas (203). Further studies revealed the presence of *M. tuberculosis* complex heat shock protein 70 (hsp70), hsp65 and hsp16 in sarcoid lymph nodes (204). Subsequent immunological investigations indicated greater peripheral blood mononuclear cell (PBMC) and BAL CD4+ T_H1 and CD8+ cellular immune responses to recombinant *Mycobacterium tuberculosis* Kat G (205, 206) and KatG peptides in patients with sarcoidosis compared to healthy controls. However, there was no difference when compared with PBMC from purified-protein derivative positive (PPD+) control subjects, which profiles a pathogenic antigen in some patients with sarcoidosis (205, 207–212). Comparison of immune responses to mycobacterial whole protein between American

and Swedish patients with sarcoidosis revealed no differences despite variations in patient phenotypic, genetic and prognostic characteristics. In addition, it was shown that although systemic T_H1 immune responses were present, KatG reactive CD4+ T_H1 cells preferentially accumulated in the lungs, consistent with a compartmentalised response (205). Patients with Löfgren's syndrome exhibited a more pronounced multifunctional cytokine profile (simultaneous IFN-γ and TNF production) towards mKatG, which stimulated higher IFN-γ production in BAL fluid and blood AV2S3+ T-cells than AV2S3- T-cells. (205, 206). A greater frequency of peripheral blood T_H1 responses have also been shown in patients with sarcoidosis compared with healthy PPD- controls following stimulation with mycobacterial heat shock proteins (209, 213, 214) and mycobacterial peptides from ESAT-6 (6 kDa early secretory antigenic target) (207–212), mycolyl-transferase antigen 85A (209, 215) and superoxide dismutase A (209, 216). It is important to note that these responses were against not only multiple mycobacterial secreted proteins, but also against multiple epitopes within a given protein. Most of these synthetic antigenic peptides were related to, but distinct from, those of *M. tuberculosis*, indicating the immune responses were directed against a distinct mycobacterial species with similar homology to *M. tuberculosis*, rather than non-tuberculous mycobacteria (144, 175). It has been postulated that the antigen(s) from this mycobacterium could be released intracellularly and persist after death of the organism, with a complex of host and mycobacterial proteins in response to the infection, leading to sarcoidosis. It has also been suggested that failure to clear non-degradable antigen/protein complexes in some patients with certain genotypes could lead to chronic disease (174, 212).

Another link with mycobacteria is the feature that those with the MHC Class II susceptibility allele, HLA-DRB*1101, have increased recognition of ESAT-6 peptides. In addition, ESAT-6 and KatG peptides presented by antigen presenting cells that were expressing DRB*1101 induced T_H1 immune responses in sarcoid T cells (208). *Ex vivo* immunologic studies can also be correlated with bioinformatics approaches to test theoretical binding affinities of epitopes derived from antigenic proteins to sarcoidosis-associated HLA molecules (217). Using high resolution HLA-typing of 149 sarcoidosis patients and 447 controls applied to bioinformatics tools, it has been shown that patients with Löfgren's syndrome express HLA-DR alleles that *in-silico* recognise significantly more *Mycobacterium tuberculosis*, *Mycobacterium avium* and *Propionibacterium epitopes* than the control population and those with chronic sarcoidosis (218).

Propionibacterium acnes has also been isolated from culture in up to 78% of sarcoid lesions (219, 220), which has suggested a role for this commensal organism in sarcoidosis. Using PCR to amplify segments of the 16S rRNA of P. *acnes* or P. *granulosum*, several authors reported isolation of propionibacterial DNA from sarcoid tissues (221–224), with a DNA signal intensity greater than surrounding non-granulomatous tissue. These initial studies were followed by a collaborative study from Japanese and European investigators that confirmed the presence of P. *acnes* and P. *granulosum* DNA in all but two of 108 sarcoidosis specimens obtained from both Japanese and European biopsies (196). T-cell proliferation in response to *P. acnes* has been shown to be greater in patients with sarcoidosis than those without sarcoidosis (221). Experiments in animal models have also shown that *P. acnes* can induce antigen-driven granulomatous inflammation (225, 226), and promote T_H1-related cytokine expression through antigen-independent innate effects, via stimulation of TLR9 (227). Greater BAL CD8+ and CD4+ T_H1 immune responses to *M. tuberculosis* ESAT-6 and *P. acnes* proteins are seen in sarcoidosis and the same study utilised mass spectrometry to localise ESAT-6 in sarcoid granulomas, but did not identify *P. acnes* (228). In contrast, another study detected T_H1 immune responses against *P. acnes* and not ESAT-6 (229), while immunohistochemistry localised *P. acnes* antigens in sarcoid granulomas and intracellularly in sarcoid Hamazaki-Wesenberg bodies (230). A recent meta-analysis of nine studies identified that 359 tissue samples from 458 patients (78.4%) with sarcoidosis were positive for *P. acnes,* which is 13- to 30-fold higher than controls, supporting an association with sarcoidosis (231). The role of *Propionibacterium* however, remains uncertain as propionibacterial DNA has also been recovered in 57% of control tissues, including evidence of immune responses to these organisms in healthy controls, suggesting that it is a common organism found in lung tissues and lymph nodes (232).

Patients with sarcoidosis also often express autoantibodies at low titres of uncertain pathological significance (1). Since no disease-specific autoantibody profile has been described, the autoantibodies are very likely the result of polyclonal hypergammaglobulinemia from generalised B-cell activation as a result of continuous CD4+ T-cell activation by 'granulomagenic' antigens. Viral infections including Epstein-Barr virus, human herpesvirus-8, Coxsackie virus, mycobacteriophage and herpes simplex have also previously been suggested as possible aetiological agents in sarcoidosis based on presence of serum antibodies, but there is little supportive evidence (116, 174, 223, 233). BAL of HLA-DRB1*0301 patients with Löfgren's syndrome was eluted and antigenic peptides bound to HLA-DR molecules from lung T-cells expressing the T-cell receptor AV2S3 gene segment identified. Strongly bound peptides identified included several potential autoantigens including ATP synthase, vimentin and lysyl tRNA synthetase (234). Subsequent T_H1 T-cell

responses were identified to these autoantigens in some of these patients. Since HLA-DRB1*0301 positive patients from Sweden usually achieve remission, it is possible that peptides bound to HLA-DRB1*0301 are derived from autoantigens that could be involved in sustaining inflammation or leading to remission (119).

These recent molecular, genetic and immunological studies support an association between mycobacteria and propionibacteria in the pathogenesis of sarcoidosis. It is also possible that the triggering antigen may vary depending on ethnicity, geographic location and individual genetic background (144). There is a need for future studies to identify whether the molecular and immunological findings are due to an actively replicating organism that is difficult to identify, or a previously cleared pathogen/antigen with residual proteins and nucleic acids present within sarcoid granulomas (175). Arguments against the former include: that Kveim-Siltzbach agent had no observed viable organisms present, although it induced a granulomatous response in most patients with sarcoidosis; and also, there is a lack of reactivation of a latent mycobacterial infection in patients receiving corticosteroids, immunosuppressive or anti-TNF therapy (203). Novel studies have also hypothesised that microbial genes encoding enzymes found in sarcoid tissues could be targeted by currently available anti-mycobacterial antibiotics which localise to sites of sarcoid granulomatous inflammation (235). Antimicrobials are however, usually ineffective in sarcoidosis, although some small studies report positive results in response to anti-mycobacterial and anti-fungal agents. The answers to these questions and the long-standing mystery of the aetiology of sarcoidosis may be unravelled through further identification of the antigens inducing the disease (143, 236).

4) Immunological features

a) Immunopathogenesis and role of key cytokines and chemokines

The hallmark of sarcoidosis is the presence of non-caseating granulomas, which undergo four different stages of formation: initiation, accumulation, effector stage and resolution or fibrosis (237). During initiation, the stimulus arises when the unknown antigenic peptide is presented to T cell receptors on naïve T cells via HLA Class II molecules on antigen-presenting cells (Figure). This results in activation of the T cells with subsequent clonal proliferation with a T_H1 polarisation, producing increased amounts of IL-2 which acts as a stimulus for the differentiation and growth of more T cells (238). During the accumulation and effector stages, other cytokines and chemokines contribute to the granulomatous inflammatory process. Interferon-γ (IFN-γ) released by the T_H1 cells and inflammatory mediators produced by macrophages (TNF-α, IL-12, IL-18, monocyte chemotactic protein-1 (MCP-1), macrophage inflammatory protein-1α (MIP-1α), CCL2, CCL4, CCL5, and CXCL10) stimulate the recruitment and activation of blood monocytes to sites of disease to form non-caseating granulomas (237, 239, 240). Amyloid A and Toll-like receptor 2 have also been implicated in the process, but TNF-α appears to be essential for granuloma development (143).

The granulomatous inflammation may eventually resolve with either complete antigen clearance (241) or IL-10-induced suppression of helper T cell and macrophage activity (242), although findings on the latter have been inconclusive (243). Fibrosis is an alternative outcome and there are two possible mechanisms. The first mechanism is a transition from a T_H1 (IL-2, IFN-γ) to T_H2 (IL-4, IL-5, IL-10, IL-13) cytokine profile. T_H1 cytokines play a role in promoting granulomatous inflammation with an inhibitory effect on fibrosis development, which is evident by the significantly higher BAL IFN-γ levels in sarcoid patients compared to healthy controls and the inverse relationship of BAL IFN-γ levels and clinical progression to pulmonary fibrosis (244). Although there is a lack of studies on the role of T_H2 cytokines in sarcoid pulmonary fibrosis, IL-13 has been known to stimulate production of transforming growth factor-β (TGF-β), which activates fibroblasts to synthesise collagen and extracellular matrix (245, 246). Other macrophage-derived factors, such as fibronectin, insulin-like growth factor (IGF-1) and platelet-derived growth factor, also play a role in the activation and proliferation of fibroblasts (247). The activation of macrophages into wound healing M2 phenotypes in a T_H2 cytokine milieu is another possible mechanism of pulmonary fibrosis in sarcoidosis as these macrophages produce profibrotic TGF-β and chemokines, e.g. CCL18, to promote collagen synthesis by fibroblasts (248, 249).

Recently, T_H17 cells have been implicated in the immunopathogenesis of sarcoidosis. Immunologically distinct from T_H1 cells, which are involved in cell-mediated immunity and T_H2 cells which contribute to humoral immunity, T_H17 cells are associated with autoimmunity and host defence against extracellular pathogens (250). Flow cytometric studies have demonstrated an increase in IL-17 and IL-23R expression by CD4+ T cells in BAL, peripheral blood, and lymph node biopsy samples of patients with active sarcoidosis compared to those with inactive disease and healthy controls (251). Increased numbers of IL-17+, IL-17+IFN-γ+, and IL-17+IL-4+ memory T cells were observed in BAL and peripheral blood

from patients with sarcoidosis (252). T_H1 and T_H17 gene expression, as well as IL-23 and IL-23R expression, were also found to be upregulated in skin biopsies obtained from patients with sarcoidosis (253), but the exact role of T_H17 cells and their cytokines remains unclear. IL-17 may additionally be produced by natural killer T cells and neutrophils (254), and a critical analysis of the involvement of T_H17 immunity in sarcoidosis is required.

b) The immune paradox in sarcoidosis

Sarcoidosis has been described as an "immune paradox" due to the presence of exaggerated T_H1-dominated inflammation and reciprocal macrophage activation at disease sites despite peripheral immunological anergy to common antigens (255, 256). Unlike normal CD4+:CD8+ T cell ratios of 2:1 in healthy controls, 50% of patients with sarcoidosis have elevated ratios ranging from 3.5:1 to 15:1 at sites of granulomatous inflammation (242, 244). Peripheral anergy in patients with sarcoidosis is characterised by T cell lymphopenia and a reduced Type IV delayed hypersensitivity immune response to recall antigens such as tuberculin in the skin (257). This may be explained by a systemic proliferation of T regulatory (Treg) cells, namely $CD4+CD25^{bright}FoxP3+$and $FoxP3^{high}CD127^-$ Treg cells, which can suppress cell-mediated immunity in the periphery but not locally at the sites of disease (247, 258, 259).This immune paradox may also be associated with the relative expression of CD28, a primary co-stimulatory molecule which stimulates interleukin-2 (IL-2) production and T cell proliferation, on pulmonary and peripheral blood CD4+ T cells of patients with sarcoidosis (260, 261). A decrease in expression of CD28 on peripheral blood T cells has been hypothesised to contribute to peripheral anergy. Some studies demonstrated CD28 down-regulation in both BAL fluid and peripheral blood of patients with chronic sarcoidosis; however, others have shown an up-regulation of CD28 expression in the BAL of patients with untreated sarcoid alveolitis (212, 261, 262). Therefore, this hypothesis remains unproved due to the conflicting evidence.

c) T-cell receptor

Sites of granulomatous inflammation in sarcoidosis demonstrate oligoclonal expansion of T cells, with a restricted repertoire of T cell receptor (TCR) αβ genes in the lungs, blood and Kveim-Siltzbach skin reaction sites (203, 263). The selective expression of a restricted variable α region (Vα) and β region (Vβ) of the TCR genes strongly supports the involvement of an antigen-specific immune response in sarcoidosis (264–266). Unlike the αβ+ TCR-expressing T cells, the proportion of γδ+ TCR-expressing T cells is generally not increased in sarcoidosis (267). There is expansion of Vα2.3 (AV2S3+) T cells in the BAL of Scandinavian patients with either the HLA-DRB1*0301 or HLA-DRB3*0101 allele (268), suggesting that the antigen is presented by either the HLA-DRB1*0301 or HLA-DRB3*0101 molecule on the antigen-presenting cell to the specific TCR (264). AV2S3+ T cells have also been associated with a better prognosis, and have most recently been phenotyped as activated effector T cells which may have the potential for antigen eradication (269).

d) T-Regulatory cells (Treg)

Treg cells play a role in the maintenance of immune homeostasis by suppressing the amplification and cytokine production of activated T cells. Treg cells undergo proliferation during active sarcoidosis, but different repressor capacities of Treg cells have been identified when isolated from sarcoid granulomas and peripheral blood, demonstrating the immune paradox of sarcoidosis (144). Treg cells isolated from sarcoid granulomatous lesions exhibited reduced repressor capacities despite increased IL-10 and TGF-β1 production, and elevated IL-4 levels which stimulates fibroblast proliferation and activates mast cells to sustain granuloma formation (259). These Treg cells are also incapable of completely inhibiting the synthesis of IFN-γ and TNF-α by T_H1 cells, thereby allowing granuloma formation (258). In addition, another study has also demonstrated impaired Treg suppressive properties by showing a decrease in mRNA expression of FoxP3, which is an essential factor for Treg immunosuppressive function, in CD4+ T cells of patients with sarcoidosis (268). In contrast, the repressor capacity of Treg cells in the peripheral blood of patients with sarcoidosis is preserved. There is also systemic amplification of Treg cells in the peripheral blood, namely $CD4+CD25^{bright}FoxP3+$ and $FoxP3^{high}CD127^-$ Treg cells, which can suppress cell-mediated immunity to give rise to sarcoid peripheral anergy (247, 258, 259).

e) Natural Killer (NK) Cells

Natural killer T (NKT) cells are a group of lymphocytes which regulate the activity of CD4+ T cells. The heightened T cell activity that characterises sarcoid granulomatous inflammation might be a result of a deficiency or impairment in function of these immunoregulatory NKT cells (270). There is a deficiency of invariant NKT (iNKT) cells in the BAL and peripheral

blood of patients with sarcoidosis, but not in those with Löfgren's syndrome (271). iNKT cells, also known as Type I NKT cells, are CD1d-dependent cells which express a highly restricted TCR with an invariant Vα24-Jα18 paired with Vβ11 (272–274). Since Löfgren's syndrome is usually associated with disease resolution, the lack of iNKT cells may account for the persistent inflammation observed in sarcoidosis (144). Furthermore, stimulation of blood NKT cells with α-galactosylceramide elicited an impaired production of IFN-γ, demonstrating a possible impairment in the cytokine-producing function of these NKT cells (275). Longitudinal analysis of the proportion and function of iNKT cells throughout the disease course is required to understand the exact role of these cells in the immunopathogenesis of sarcoidosis (270).

PATHOLOGY

1) The sarcoid granuloma

The histopathological hallmark of sarcoidosis is the formation of non-caseating granulomas at the sites of disease. These granulomas are formed as a result of cell-mediated immune responses against specific antigens, which have yet to be identified. Sarcoid granulomas are characterised by a central core of epithelioid cells, giant cells and CD4+ type 1 helper T cells (T_H1), surrounded by a peripheral zone of CD8+ T lymphocytes, B cells and fibroblasts. Epithelioid cells are activated tissue macrophages but are given the name due to their resemblance to epithelial cells under light microscopy. Electron microscopy has demonstrated the secretory function of epithelioid cells, because they possess numerous cytoplasmic projections with interdigitations (1). They secrete angiotensin-converting enzyme and an elevated serum ACE level is associated with sarcoidosis, although not specific as a screening tool (276). Upon exposure to specific antigens and subsequent antigenic stimulation, monocytes are recruited to the site of disease. In the absence of complete antigen clearance, the monocytes accumulate and eventually mature into epithelioid cells. Following cell-mediated immune responses, T lymphocytes are also recruited and infiltrate into the aggregation of epithelioid cells, forming a granuloma. A sarcoid granuloma is a dynamic structure as its periphery continuously receives newly recruited monocytes, which gradually penetrate the core where maturation into epithelioid cells occurs (277). After several months or years, the granuloma may resolve when epithelioid cells exit via the periphery into the surrounding tissues, sometimes leaving behind fibrotic changes (278).

Recently, the lymphatic drainage of pulmonary sarcoid granulomas has been widely studied to explain the role of pulmonary lymphatics in the drainage of alveolar fluids and their possible involvement in the immunopathogenesis of sarcoidosis. Because sarcoidosis commonly involves the lungs and intra-thoracic lymph nodes, it has been postulated that an airborne antigen might be the trigger for the disease (279, 280). Common locations of pulmonary sarcoid granulomas are areas near peribronchovascular bundles, in interlobular septa, along subpleural connective tissues and within lobular parenchyma. Sarcoid granulomas can also, although less commonly, be found in other organs such as liver, spleen, skin and brain (281). Some studies highlighted the role of pulmonary lymphatics in granuloma formation after alveolar processing of airborne pathogens. An experiment, which involved infecting guinea pigs with *Mycobacterium tuberculosis*-containing aerosols, demonstrated the selectivity of connective tissue spaces between alveolar membranes and lymphatic vessels for inflammatory cell infiltration, ultimately giving rise to epithelioid granulomas (282). Another investigation on lung biopsy samples did not observe any lymphatics within sarcoid granulomas but did note that most intralobular and perilobular granulomas were adjacent to at least one lymphatic vessel, suggesting the role of lymphatics in the mobilisation of inflammatory cells to form granulomas. This study also demonstrated the avascularity of a large majority of pulmonary sarcoid granulomas as CD31 and CD34 blood capillary immunolabelling demonstrated confinement of microvasculature to the outer border of the peripheral fibrous zone of the granulomas (283). This gives rise to "hypoxic granuloma" in sarcoidosis, which may hinder the distribution of systemic therapeutic agents used to treat the granulomatous lesions.

2) Histological diagnosis

Due to the lack of an adequately sensitive and specific diagnostic test, the diagnosis of sarcoidosis is based on three different criteria: (i) compatible clinico-radiological findings, (ii) histological evidence of non-caseating granulomas

on tissue biopsy, and (iii) exclusion of other possible diagnoses (1). Histologic examination of tissue biopsy is part of the multi-process diagnostic approach for sarcoidosis. Although there is no definitive diagnostic feature of sarcoid granulomas, certain histological characteristics may point towards a diagnosis. A sarcoid granuloma usually consists of a compact core of epithelioid and multinucleated giant cells. There is also absence of necrosis, or at most a small amount of necrosis, despite it being typically characterised as a non-caseating granuloma. In the periphery of the granuloma, a zone of lymphocytes is also found. Inclusion bodies, such as Schaumann's bodies, asteroid bodies, birefringent crystals, and Hamazaki-Wesenberg bodies, may occasionally be seen but they are non-specific to sarcoidosis. Granulomata are generally a non-specific inflammatory reaction as tumour-related "sarcoid reactions" can also produce non-caseating epithelioid cell granulomas (1). Therefore, it is important to understand that histological evidence of granuloma alone is non-diagnostic of sarcoidosis or any other granulomatous disease, and needs to be combined with other clinical and laboratory findings (284). Every biopsy sample should be tested for alternative causes of granulomatous inflammation, such as mycobacteria, fungi (e.g. histoplasma), parasites, and foreign particles like beryllium (285).

Exclusion of other granulomatous diseases requires a multifaceted approach. Besides microscopic examination of tissue, microbiological studies of the biopsy sample should also be performed, especially in the presence of necrosis. This involves special stains for certain potentially pathogenic micro-organisms, such as mycobacteria (acid-fast bacilli stain) and fungi, and microbial cultures (286). If a detailed medical history indicates occupational exposure to chemicals such as beryllium, a beryllium lymphocyte proliferation test for chronic beryllium disease may be performed (287). Antibody testing for hypersensitivity pneumonitis is also required when there is identified significant environmental exposure to organic dusts or birds (288). The Kveim-Siltzbach test used to be a diagnostic test for sarcoidosis but is no longer in use. It was performed by intradermal inoculation of a splenic or lymph node sarcoid tissue suspension, and the resultant papule biopsied four to six weeks later for detection of non-caseating granulomas, which would indicate sarcoidosis (289). The use of this test has been limited by its varying sensitivity and specificity due to the different sarcoid tissues used in testing and risks of transmission of infection due to the use of human tissue samples (290).

CLINICAL PRESENTATION AND ORGAN INVOLVEMENT

Sarcoidosis is often a multi-system disorder and can present with diverse clinical manifestations, which means patients usually present to clinicians in different specialties. Sometimes specific and organ-limited syndromes characterise the presentation such as Löfgren's syndrome and Heerfordt's syndrome. The clinical presentation of the disease may depend on genetic and/or ethnic factors, disease duration, site and extent of organ involvement as well as disease activity (1). The extent of disease and organs involved will often influence treatment decisions.

1) Systemic Constitutional Features

Patients often report a prolonged period of illness and investigation prior to a diagnosis of sarcoidosis, being made on the first physician visit in only 13.5% of cases in one study (291). This often occurs because many patients have non-specific constitutional symptoms including fever, fatigue, general malaise, anorexia, weight loss, sleep disturbance and depression which can occur in one third of patients with sarcoidosis and are associated with raised C-reactive protein. Fatigue is under-recognised and may be present in up to two-thirds of patients. It can be very disabling, resulting in negative effects on quality of life (292–294). Incapacitating fatigue may also be present and persist even when the disease has gone into remission, in what is referred to as the "post-sarcoidosis chronic fatigue syndrome", which also includes clinical features of wide-spread myalgia, sleep disturbance and low mood (295–297). Fever is generally low grade, but temperature elevations up to 39 to 40°C may be seen. Sarcoidosis has also been identified as an overlooked cause of fever in patients with pyrexia of unknown origin (298). Weight loss is usually limited to 2-6kg during 10-12 weeks prior to clinical presentation. Constitutional symptoms are more frequent in African-Americans and Asian Indians than in Caucasian patients with sarcoidosis (1).

2) Specific Organ Involvement:

a) Respiratory tract, pulmonary and thoracic lymph node involvement

Intrathoracic involvement occurs in more than 90% of patients with sarcoidosis, including mediastinal lymphadenopathy, respiratory tract and lung involvement. Respiratory symptoms in sarcoidosis often include dyspnoea, dry cough, vague chest discomfort, exercise limitation and wheezing and occur in one-third to one-half of all patients. Haemoptysis is rare. One third or more of patients are asymptomatic, with incidental abnormalities on chest radiographs, although in rare cases other patients may have a chronic, progressive and sometimes fatal course, with respiratory failure. Massive hilar and/or mediastinal lymphadenopathy may also cause fatigue, dysphagia and retrosternal pain in some patients (299, 300). On clinical examination, clubbing occurs rarely and pulmonary crackles occur in <20% of patients (1).

Pulmonary sarcoidosis also often first comes to attention when abnormalities are found on a chest radiograph during a routine screening examination. Chest radiographs are used in the initial assessment of patients with respiratory symptoms or when a diagnosis of sarcoidosis is suspected. The chest radiograph patterns and appearances have been classified according to a "staging system", with four stages described by Scadding in 1961 (15). Stage I involves bilateral hilar lymphadenopathy without infiltration that may be associated with paratracheal lymphadenopathy, Stage II bilateral hilar lymphadenopathy with pulmonary infiltrates, Stage III pulmonary infiltrates alone and Stage IV is characterised by pulmonary fibrosis, with features including fibrotic bands, bullae, hilar retraction, bronchiectasis, honeycombing and diaphragmatic tenting (106). Unilateral hilar lymphadenopathy is also observed in 3-5% of patients. Mediastinal lymphadenopathy in the absence of hilar lymphadenopathy is rare and usually indicates an alternative diagnosis (276). The so-called stages represent radiographic appearances and do not necessarily progress from one stage to another or correlate with disease chronicity or changes in pulmonary function (301). Around two-thirds of patients have abnormal lung function at clinical presentation, with pulmonary function tests usually indicating decreased diffusing capacity and restrictive ventilatory dysfunction, with reduced forced vial capacity (FVC) and reduced forced expiratory volume in 1 second (FEV_1) (302, 303).Although pulmonary parenchymal involvement is the most common, the airways, including larynx, trachea and bronchi may be involved, leading to airway obstruction and bronchiectasis. Around half of patients also have obstructive airway disease, with a reduced ratio of FEV_1 to FVC and some have bronchial hyper-responsiveness (50,304). Endobronchial involvement significantly increases the risk for airway hyper-reactivity, which occurs in up to 83% of patients (305). In about 80% of patients who have abnormal spirometric findings, values usually return within the normal range within 2 years (301). In 10-20% of patients with pulmonary sarcoidosis, the granulomatous inflammation becomes chronic with concomitant healing and inflammation, ultimately leading to pulmonary fibrosis (306). Other uncommon manifestations include pleural effusions, chylothorax, pneumothorax, granulomatous pleural thickening and calcification, lymph node calcification and pulmonary cavitation with mycetomas (1).

The diffusing capacity of the lung to carbon monoxide (DLCO) reflects the ventilation-perfusion deficit seen in the mismatch caused by parenchymal lung disease but also declines if pulmonary hypertension (PH) develops.

The pulmonary artery pressure is elevated in 6-23% of selected patients at rest and up to 43% of patients with exertion (307). Pulmonary fibrosis with chronic hypoxaemia and involvement of pulmonary vessels is the most common mechanism for development of pulmonary hypertension; although granulomatous infiltration of pulmonary arterioles or left ventricular dysfunction can cause PH in the absence of pulmonary fibrosis (308, 309). This is an important cause of unexplained breathlessness in patients with sarcoidosis in the absence of pulmonary fibrosis (310). Pulmonary hypertension significantly worsens the prognosis, with an associated five-fold increased mortality in patients with sarcoidosis who have advanced pulmonary disease (311, 312). In a small case series, prostacyclin analogues, endothelin receptor antagonists and phosphodiesterase-5 inhibitors have been shown to improve haemodynamics, functional status and clinical outcomes (313). A recent study demonstrated that patients with sarcoidosis receiving PH treatment had beneficial reductions in pulmonary artery pressure, with improvements in exercise tolerance and 6-minute walk distance (307, 314). However, the numbers were small, some had PH secondary to Stage IV fibrosis, while others had PHT secondary to sarcoid-related vasculopathy. The effect of pulmonary vasodilator therapy on patient survival remains uncertain (315).

b) Lymphoid and haematological involvement

Approximately one-third of patients with sarcoidosis have palpable peripheral lymphadenopathy. The most commonly involved nodes are cervical, axillary, epitrochlear and inguinal. In some people, the lymphadenopathy can be extensive, particularly in some ethnic groups (316). In the neck, the posterior triangle nodes are more frequently affected than in the anterior triangle (1). Enlarged lymph nodes are discrete, mobile, non-tender and typically do not ulcerate or form draining sinuses. Splenic involvement is discussed below; however, splenomegaly is usually minimal and silent but it may rarely lead to pressure symptoms, anaemia, leukopenia and thrombocytopenia (317). Anaemia occurs in 4-20% of patients with sarcoidosis and leukopenia in up to 40% of patients, although it is rarely severe (318). In the absence of splenomegaly, leukopenia may reflect bone marrow involvement. Peripheral blood lymphocytopenia is a common abnormality in sarcoidosis (261) as the activated T-cells accumulate to sites of granulomatous inflammation (319). Other haematological abnormalities such as eosinophilia, neutropenia or autoimmune haemolytic anaemia and/or thrombocytopenia are rare (278).

c) Skin Involvement

Whilst thoracic disease is the most common manifestation, skin involvement occurs in at least 20-30% of patients and is often missed (276). Sarcoid skin lesions, although not life threatening, can be emotionally devastating, particularly if affecting the face, and affect quality of life (106). Cutaneous sarcoidosis often presents as isolated lesions or in crops and is often attributed to other causes, usually due to the highly variable manifestations, such as plaques, macules, papules, nodular, psoriatic-like and hyper- or hypopigmented lesions. Lesions are usually present on the nape of the neck, upper back, extremities and trunk (106). Careful dermatological examination is needed as skin biopsies of suspected sarcoid lesions have a high diagnostic yield (276). It is also important to review surgical scars and tattoos as these are often infiltrated by sarcoid granulomas (Koebner type reaction), are easy to biopsy and may be the presenting feature of generalised sarcoidosis. These lesions frequently occur on the face and neck (256, 320, 321).

Erythema nodosum is a hallmark of sarcoidosis, occurring in ~10% of patients and usually lasting for ~6-8 weeks (106). It is characterised by raised, erythematous painful nodules in the lower extremities, with an acute presentation that occurs more commonly in women of childbearing age usually in European patients. It usually has a good prognosis with spontaneous recovery, as in most cases of Löfgren's syndrome. Biopsy specimens of erythema nodosum often display non-specific septal panniculitis, which does not confirm a diagnosis of sarcoidosis as it may be present in other granulomatous and non-granulomatous conditions. Lupus pernio is pathognomonic for sarcoidosis and refers to sarcoid-related indurated, lumpy, violaceous lesions on the cheeks, nose, lips and ears and is also a recognised feature in more chronic disease, pulmonary fibrosis and with extrapulmonary involvement (322). Although infrequent, it often affects elderly female patients, especially West Indians and African Americans, and can be disfiguring, eroding into underlying bone and cartilage (323). Lupus pernio also appears more commonly in patients with African and Polynesian ancestry, as are other non-pulmonary manifestations (316).

d) Ocular Involvement

The eye is the third most commonly affected organ in sarcoidosis, with higher occurrence rates among the African American, Japanese and female populations (324). Ocular involvement is most frequently bilateral. Although granulomatous inflammation can either occur within the eye or in adnexal structures, uveitis is the most common sarcoid eye lesion (325). It can be anterior, intermediate or posterior uveitis. One-third of patients with uveitis may be asymptomatic, while others may present with conjunctival injection, pain, photophobia and tearing (326). Ophthalmologists are usually well aware of ocular sarcoidosis as a diagnosis, and assess their patients with a serum ACE and chest x-ray as screening tools, but the reverse review can sometimes be forgotten by respiratory physicians, particularly when the eye disease is asymptomatic.

The more insidious-presenting chronic anterior uveitis is more common than the acute pain and photophobia from acute anterior uveitis (327). As untreated uveitis can lead to permanent visual impairment, the 1999 ATS/ERS/WASOG statement on sarcoidosis recommended an initial ophthalmologic evaluation for all patients diagnosed with sarcoidosis (1). Other ocular presentations include lacrimal gland infiltration, palpable orbital mass, retinal periphlebitis and optic disc abnormalities (328, 329). In conjunction with laboratory and radiological studies, the international criteria for the diagnosis of intraocular sarcoidosis includes seven clinical signs: 1) mutton-fat keratic precipitates (KPs), small granulomatous KPs

and/or iris nodules (Koeppe/Busacca), (2) trabecular meshwork nodules and/or tent-shaped peripheral anterior synechiae (PAS), (3) vitreous opacities displaying snowballs/strings of pearls, (4) multiple chorioretinal peripheral lesions (active and/or atrophic), (5) nodular and/or segmental peri-phlebitis (+/- candlewax drippings) and/or retinal macroaneurysm in an inflamed eye, 6) optic disc nodule(s)/granuloma(s) and/or solitary choroidal nodule, and (7) bilaterality (325).

It is therefore important for respiratory physicians to ensure that all patients with suspected ocular sarcoidosis have an initial ophthalmological review, and generally at least an annual or bi-annual review is prudent while the disease is active. At each respiratory clinical review, it is recommended that there is an inquiry for symptoms of ocular pain or blurred vision and that the eyes are inspected for any visible inflammation.

e) Cardiac Sarcoidosis

When assessed by post-mortem studies in selected patients, cardiac sarcoidosis is more common than clinically identified in life. Myocardial sarcoid granulomas have been found at autopsy in up to 20-30% of patients with chronic sarcoidosis (330–332); although fewer than 5% of patients suffer from clinical disease (333). Cardiac sarcoidosis is more common in Japanese patients, with an incidence up to 60% in specialist centres, where it accounts for many deaths as a result of sarcoidosis (334).

Cardiac sarcoidosis can affect any part of the heart and conduction system, with a predilection for the left ventricular wall myocardium, followed by the interventricular septum and conducting system, although the pericardium and endocardium may be involved (333). Sarcoid granulomas with development of subsequent fibrosis may infiltrate the myocardium and the conducting system. This results in a wide spectrum of manifestations including aberrations of atrioventricular or intraventricular conduction with either silent or symptomatic heart block, valvular dysfunction, pericardial effusions and tamponade, ventricular arrhythmias, as well as congestive heart failure and sudden cardiac death, presumably from dysrhythmias (333, 334).

There is currently no validated approach to screen for cardiac sarcoidosis, although a comprehensive medical history with review of cardiac symptoms, physical examination and electrocardiographic (ECG) examination is needed during initial evaluation. Abnormal physical examination or ECG findings warrant further investigations, including echocardiography, ambulatory cardiac event monitoring and further imaging studies (330). Unfortunately, no gold standard exists that would allow a confident diagnosis of cardiac sarcoidosis, with a lack of an evidence-based diagnostic approach to disease. Thallium-201, technetium-99m, and gallium-67scintigraphy has been used (335), although recently positron emission tomography (^{18}F-FDG PET) scanning has been shown to be most sensitive (336, 337). Coronary angiography is needed to exclude coronary artery disease if nuclear medicine imaging shows cardiac involvement. Delayed contrast enhanced cardiac magnetic resonance imaging (MRI) may detect small amounts of sarcoid-related cardiac damage (338). Cardiac MRI may be theoretically useful in evaluation of patients on anti-inflammatory treatments, which may reduce fluorodeoxyglucose uptake and theoretically reduce ^{18}F-FDG PET sensitivity (327). However, the decision whether to initially use ^{18}F-FDG PET scanning or cardiac MRI in the diagnosis of cardiac sarcoidosis remains controversial. In patients with suspected or proved sarcoidosis, who are likely to need a pacemaker, it is desirable to obtain a cardiac MRI because this may often be contraindicated once a pacemaker is inserted. Electrophysiological studies are helpful in investigating patients with syncope or significant ECG abnormalities; however, the sensitivity and ability to risk stratify patients is not well defined. A normal electrophysiological study at any point in time does not exclude future granulomatous infiltration and development of fibrosis in critical areas of myocardium. Endomyocardial biopsy may be used for histological diagnosis; however, it is an invasive procedure that lacks sensitivity and which has a low diagnostic yield. This is usually because granuloma formation tends to be patchy and more often involves the lateral and basal left ventricle rather than the right ventricle, where biopsies are commonly performed (106, 339). Results from endomyocardial biopsy specimens are positive in <10% of patients and hence a positive cardiac biopsy in not required to make a diagnosis of cardiac sarcoidosis (333, 340). An approach to screening for cardiac sarcoidosis is suggested under 'Investigations' below.

As cardiac sarcoidosis can develop in the absence of apparent disease elsewhere, sarcoidosis should be considered in any non-ischaemic form of cardiomyopathy, particularly when rhythm disturbances are present (327). Important prognostic indicators include New York Heart Association functional class, presence of left ventricular enlargement and sustained ventricular tachycardia (333).

f) Neurosarcoidosis

Neurosarcoidosis is usually clinically rare, although a potentially devastating complication when it affects the central nervous system (CNS). Neurosarcoidosis is detected at autopsy in up to 25% of patients and can occur in the absence of apparent disease elsewhere (276). Neurological disease may be the only manifestation in 10-17% of patients with sarcoidosis (341) and is present in ~10% of patients with multisystem disease (342).

Common symptoms of neurosarcoidosis include cranial nerve palsies, particularly of the facial nerve, ataxia, cognitive dysfunction, neuropsychiatric symptoms, headaches, seizures and weakness (343, 344). Seizures have been reported in 5-22% of patients with neurosarcoidosis and are associated with disease chronicity and increased risk of death (345). CNS involvement may include leptomeningeal disease with aseptic meningitis or meningeal infiltration, hypothalamic involvement presenting with pituitary insufficiency, pituitary involvement often presenting with diabetes insipidus (346), encephalopathy, vasculopathy, hydrocephalus and space-occupying lesions (347). Effects on the peripheral nervous system include cranial nerve palsies, most commonly optic nerve and/or unilateral facial nerve involvement presenting with Heerfordt's syndrome, as well as peripheral or small fibre neuropathy (256). The mechanism of cranial nerve palsies is unclear, although cranial nerve polyneuritis or demyelination and sarcoid lesions at the brainstem level have been suggested (345). Evidence of small fibre neuropathy has been reported in patients with unexplained pain and dysaesthesia (348). Spinal cord involvement has also been described and can result in paraplegia and quadriplegia, which also has a poor prognosis (276, 349).

Neurosarcoidosis can mimic other neoplastic, inflammatory, infectious and demyelinating nervous system disorders. Diagnosis can be difficult and usually relies on indirect information from imaging, cerebrospinal fluid (CSF) examination and histological evidence of disease from extraneural tissue biopsy (349). Analysis of CSF in patients with CNS involvement indicates non-specific lymphocytosis. Measurement of CSF CD4+/CD8+ T-cell ratios, lysozyme, β_2-microglobulin and ACE levels have been suggested as an aid to diagnosis (347), with high CSF ACE specificities reported in one study (350), although this remains controversial as serum ACE activity levels are neither specific nor sensitive for diagnosis (341). In one third of patients, oligoclonal immunoglobulin bands are elevated in the CSF, which may represent non-specific B-cell activation and makes it difficult to differentiate neurosarcoidosis from multiple sclerosis (341). CSF examination is useful in excluding tuberculosis and fungal infection. Although MRI with gadolinium contrast remains the most sensitive technique for detecting neurosarcoidosis and guiding therapy, other investigations, including ^{18}F-FDG PET scanning and cerebrospinal fluid examination, can provide important information.

Reports of the anti-tumour necrosis factor-α agent infliximab suggest that this drug may be helpful for patients with refractory neurosarcoidosis (351); however, further randomised control trials are required to assess the efficacy of these biological agents (352, 353). Treatment of neurosarcoid lesions that are evident on MRI should be continued until resolution occurs, as assessed with repeat MRI scans, but it can be difficult to manage, and treatment may be aimed more at stability rather than resolution.

g) Liver and spleen involvement

Liver biopsies may reveal granulomatous involvement in up to 40-70% of patients with sarcoidosis, mostly ranging from asymptomatic incidental granulomas to portal hypertension from involvement of the portal triad with relatively preserved liver function (354). Although rare, clinically significant hepatic dysfunction can occur (276) and is at least twice as common in African Americans compared to white Americans (355). Up to one third of patients have hepatomegaly or a cholestatic pattern of liver function test derangement, with ~10% of patients with sarcoidosis having elevated serum aminotransferase and alkaline phosphatase concentrations (50).

A cholestatic syndrome characterised by pruritis, jaundice, hepatic failure, portal hypertension or even Budd Chiari syndrome can develop in rare cases; however, liver involvement is mostly clinically silent. Intrahepatic cholestasis may resemble that of primary biliary cirrhosis or sclerosing cholangitis. Histologically, hepatic sarcoid may resemble granulomatous disease from primary biliary cirrhosis, tuberculosis and other infectious diseases, chronic inflammatory bowel disease, Hodgkin's disease, chronic active hepatitis and rarely carcinoma (356). Detection of liver and splenic lesions has been found in 5% and 15% of patients on computed tomography (CT) imaging respectively (357). CT scans often show hepatosplenomegaly and lymphadenopathy, as well as focal low-attenuation lesions of the liver and spleen. Ultrasonic transient elastography ('Fibroscan') can be used can now be used to detect fibrosis and cirrhosis, which is largely

replacing liver biopsy unless there is doubt about the cause of the hepatic dysfunction. Significant liver involvement in sarcoidosis correlates with constitutional symptoms including fever, night sweats, anorexia, arthralgia and weight loss in up to 60% of patients. Ascites is usually a transudate from right heart failure (secondary to pulmonary hypertension) or portal hypertension (due to biliary cirrhosis). Rarely, an exudative ascites may occur from involvement of the peritoneum with nodules (354). Other manifestations of decompensated liver disease with portal hypertension leading to variceal bleeding, hepatopulmonary syndrome with refractory hypoxemia and liver cirrhosis occur rarely in 1% of cases (356).

h) Renal Sarcoidosis

Granulomatous inflammation of the kidneys can be found in 7-23% of patients with sarcoidosis and rarely progresses into renal failure (328). The most common histological finding is granulomatous interstitial nephritis (1, 358), usually associated with biochemical aberrations of calcium metabolism which present as hypercalcaemia, hypercalciuria, nephrocalcinosis and nephrolithiasis (359). Although renal disease is uncommon, increased serum creatinine and urea levels may reflect renal impairment secondary to chronic hypercalcaemia, hypercalciuria, nephrolithiasis, nephrocalcinosis or granulomatous interstitial nephritis (360–362). In a minority of patients with systemic sarcoidosis, pain from nephrolithiasis may be the first clinical sign (363). Proteinuria, microscopic haematuria and sterile pyuria may also occur in some patients with renal involvement (360). Rarely, renal sarcoidosis may appear as a granulomatous pseudotumour in either one or both kidneys, resulting in a misdiagnosis of renal malignancy (364).

i) Musculoskeletal System

Sarcoidosis can affect muscles, bones, and joints. Non-caseating granulomas are seen histologically in muscles and synovium, while lytic, permeative ('moth-eaten') and destructive lesions are found in bones (328). Sarcoid myopathy can present as acute myopathy, chronic myopathy or nodular myopathy. Chronic myopathy is most common and classically causes symmetrical proximal weakness (365). Nodular myopathy is uncommon and usually only causes myalgia without weakness. Nodular accumulation of granulomas in dense connective tissues may sometimes resemble tumours. Acute myopathy is least common and is characterised by a rapid onset of myalgia and proximal weakness, often associated with fever, lasting for several weeks. Since corticosteroids are the mainstay treatment for sarcoidosis, steroid-induced myopathy should be excluded (1).

The small bones of the hands and feet are most commonly affected in sarcoidosis as a dactylitis, whereas involvement of the calvarium, vertebrae, ribs, pelvis and long bones are less frequent. Most patients remain asymptomatic except for those with vertebral involvement who may complain of back pain (366). Since bony sarcoid lesions are usually an incidental finding, the reported incidence of skeletal sarcoidosis at 5-39% may be an underestimation (367).

Sarcoid arthritis, bilateral hilar lymphadenopathy, and erythema nodosum occur concomitantly in Löfgren's syndrome. Ultrasonographic examination has revealed periarthritis, rather than a true arthritis, that most frequently affects the ankles, knees and wrists and does not cause joint destruction (328). Rarely, an overlap syndrome may be seen with systemic sclerosis (368)

j) Salivary Glands

Sarcoidosis involves the parotid glands in approximately 6% of cases. It manifests as parotitis and parotid gland enlargement, and if concomitant symptoms of fever, uveitis and facial nerve palsy are present, it is termed Heerfordt's syndrome (1, 369). This syndrome has a peak incidence around ages 20-40 and affects women more than men (370). Since parotid gland enlargement is also found in other conditions such as Sjögren's syndrome, bacterial and viral parotitis, a tissue biopsy may be needed (371).

k) Gastrointestinal Tract

Gastrointestinal tract involvement in sarcoidosis is rare. However, when it occurs, it most typically affects the gastric antrum and less frequently the oesophagus, appendix, rectum and pancreas (354). Presenting symptoms include nausea, abdominal pain, early satiety and weight loss. Obstructive symptoms, even in the absence of gut wall involvement, may arise due to external compression by granulomas or enlarged lymph nodes. Sarcoid infiltration of the pancreas may occur diffusely or in the head of the pancreas, rarely causing obstructive jaundice, abdominal pain, anorexia or increased

serum lipase levels (328). The diagnosis of gastrointestinal sarcoidosis is difficult due to its rare occurrence and similar histology to other granulomatous inflammatory conditions such as Crohn's disease and tuberculosis (372).

l) Endocrine Glands

Hypercalcaemia occurs in 10-20% of patients with sarcoidosis due to excess conversion of 25 (OH) vitamin D to 1,25 $(OH)_2$ vitamin D by macrophage 1-α-hydroxylase within sarcoid granulomas (328). The hydroxylated vitamin D stimulates intestinal calcium absorption and bone resorption, increasing serum calcium levels. Hypercalcaemia is more pronounced in sarcoid patients living in the Northern hemisphere during summer periods due to longer duration of sunlight exposure, which stimulates cutaneous vitamin D production (373). Hypercalcaemia in turn predisposes the development of hypercalciuria which may result in nephrocalcinosis, nephrolithiasis and even renal failure (359). Other complications of sarcoidosis involving hypercalcaemia include thirst, dehydration, altered consciousness and osteoporosis. For patients who require long-term corticosteroid treatment, which may also cause osteoporosis, bone protection therapy is recommended (373).

Sarcoidosis of the thyroid gland is uncommon. According to post-mortem studies, it occurs in 4.2-4.6% of patients with sarcoidosis and more frequently affects middle-aged women (374). It usually causes hypothyroidism because of fibrosis of thyroid parenchyma or impaired secretory function of thyroid cells. Hyperthyroidism or euthyroid thyroiditis may also result (375). The exact disease mechanism is unknown although some proposed that thyroid dysfunction in sarcoidosis is due to autoimmunity rather than sarcoid infiltration (373).

Sarcoid involvement of the pituitary gland and hypothalamus may cause diabetes insipidus, syndrome of inappropriate antidiuretic hormone secretion (SIADH) and impaired secretion of anterior pituitary hormones. Adrenal glands are rarely affected in sarcoidosis but may cause adrenal insufficiency or adrenal failure secondary to hypothalamic-pituitary dysfunction as a result of sarcoid infiltration (373).

m) Reproductive Glands

Sarcoidosis of the female reproductive tract accounts for <1% of all cases, mostly occurring in the reproductive ages of 20-40 years old. The uterus is the most commonly involved organ of the female genital tract, affecting both the endometrium and myometrium. Most experience menstrual irregularities, menorrhagia, post-menopausal bleeding or amenorrhoea and some may have no symptoms (376). Ovarian sarcoidosis may present non-specifically as fever, malaise and abdominal pain, or with clinical features suggestive of ovarian tumours such as ovarian mass, obstructive uropathy and ascites. The fallopian tubes may also be involved and only a few cases of vaginal sarcoidosis have been reported to date (377,378). There appears to be no adverse effect on conception, pregnancy and delivery of a healthy baby despite possible granuloma formation in the placenta (373,376).

The male reproductive tract is rarely affected in sarcoidosis, with a frequency of <0.2%. The epididymis is most commonly involved, followed by testis, prostate gland, spermatic cord, scrotum and penis (379). Some male patients may be asymptomatic, while others may present with painless scrotal mass, testicular swelling or acute epididymo-orchitis. Since the peak incidence is around 30 years of age, which coincides with that of testicular malignancy, a high index of suspicion for possible malignancy should be adopted. It is thought that genitourinary sarcoidosis in men may lead to oligospermia and infertility due to fibrosis and occlusion of the ductus epididymis (373).

n) Sinonasal disease

Sarcoidosis of the upper respiratory tract has been reported with a prevalence of between 2 and 10% (380, 381). It appears more common in Pacific and Maori patients and in the absence of classic pulmonary disease can be mistaken for culture negative tuberculosis or ANCA associated vasculitis (316). Common presenting symptoms include nasal stuffiness, crusting and nasal discharge. In advanced disease epistaxis and saddle nose deformity can be evident. Laryngeal disease, which rarely can occur independently of pharyngeal involvement, is less common and patients can present with dysphonia and/or stridor (382,383). Extension of the disease to the orbit or base of brain has been reported (380). Patients with sinonasal disease are more likely to have associated lupus pernio. The diagnosis of sinonasal disease is best secured by

CT or MRI followed by upper airway endoscopy and biopsy of abnormal tissue for culture and histological examination (384). ^{18}F-FDG PET /CT enables complete mapping of active inflammation with better sensitivity compared with ^{67}gallium scintigraphy.

o) Psychosocial Effects of Sarcoidosis

Depression is common in sarcoidosis with a reported prevalence ranging from 27-66% (385,386) but anxiety, with a prevalence of 32% in one study, has been less commonly studied (387). Fatigue is a common and important symptom in sarcoidosis and is associated with a poorer quality of life and a high prevalence of both depression and anxiety (388). There are now validated instruments for assessing the qualitative impacts of sarcoidosis including the Fatigue Assessment Score (FAS) which was developed using a sarcoid population. This self-administered 10 question, 50 point instrument has a minimal clinically important difference of 4 points allowing it to be used in regular clinical practice (388–392). Two sarcoid specific quality of life instruments have been developed. The Sarcoidosis Health Questionnaire (SHQ), a 120 item self-administered questionnaire, contains only items that sarcoid patients feel are important and it has been validated in populations outside of North America, including New Zealand (393–395). More recently the King's Sarcoidosis Questionnaire (396) has been shown to correlate with pulmonary function measurements but such relationships are weak as they are with the SHQ. Fatigue has a strong relationship with quality of life whether measured with a generic instrument such as SF 36, or sarcoid specific (296).

Perceptions of illness impact on psychological wellbeing in sarcoidosis but do not necessarily correlate with the clinical severity of disease (387). The longer the disease duration the less the patient perceives that treatment will control it and females experience greater emotional distress. Clinicians do need to understand that perceptions of illness do not always align with clinician perceptions of disease state and there are undoubtedly patients who would benefit from non-pharmacologic interventions to alleviate their emotional distress.

p) Sarcoidosis in Children

The distribution of organs involved in sarcoidosis varies among children of different age groups. Children less than 5 years old usually present with a typical triad of skin rash, arthritis and uveitis, without pulmonary involvement. However, older children have similar clinical manifestations as adults, commonly in the eyes, lymph nodes and lungs (397,398). Although renal involvement is rare in children, the first case of renal sarcoidosis and Budd-Chiari syndrome in children has been reported in 2012 (399). Children diagnosed with sarcoidosis generally have a better prognosis than adults (1).

q) Sarcoidosis in Pregnancy

There is no evidence to prove an increased risk of spontaneous abortions, congenital foetal abnormalities and maternal and neonatal complications in patients with sarcoidosis during pregnancy. However, the severity of granulomatous inflammation varies, with overall improvement during pregnancy and possible reactivation during the post-partum period (400, 401). During pregnancy, oestrogen and free plasma cortisol levels increase, resulting in depressed T_H1-mediated inflammation, hence improving the clinical symptoms and signs of active sarcoidosis. After parturition, the cortisol levels decrease back to non-pregnant levels which may cause a relapse. Despite this, there have been reports of a few women with active sarcoidosis developing more progressive disease during pregnancy (402). If symptoms of sarcoidosis worsen during pregnancy and require corticosteroid therapy, the patient should be monitored carefully for glucose intolerance and infectious complications (403). The physiological changes in calcium metabolism during pregnancy, which serve to supply adequate calcium to the foetus, may additionally aggravate the sarcoidosis-related calcium derangements. However, this entity has yet to be extensively studied (401). After delivery, all patients should be evaluated routinely to monitor for a relapse in disease (403).

DIAGNOSIS

1) Blood tests and biochemistry

A compatible clinico-radiological presentation with histopathology showing non-caseating granulomas is the most convincing method of diagnosis. ACE is produced by the epithelioid cells of sarcoid granulomas, and serum ACE level is frequently measured by clinicians to reflect the total granuloma burden in patients with sarcoidosis. However, the use of serum ACE as a potential diagnostic and prognostic biomarker for sarcoidosis remains controversial due to its lack of sensitivity and specificity. The positive predictive value was 84% and negative predictive value 74% in one series (404). Serum ACE level is only increased in 60% of patients with sarcoidosis and may also be elevated in other conditions such as Gaucher's disease, disseminated tuberculosis, hyperthyroidism and fungal infections, as would be expected for a marker of activated macrophages (405). It is decreased if ACE inhibitors are used. The use of the serum ACE level as a prognostic marker is also limited as it correlates poorly with disease activity (203). Furthermore, serum ACE level is influenced by ACE gene polymorphisms. Genotype-corrected reference values of serum ACE may therefore facilitate diagnostic interpretation (406). Despite these limitations serum ACE measurement is often used in the context of a high pre-test probability in conjunction with other investigations to confirm the diagnosis of sarcoidosis. Other tests such as chitotriosidase, the soluble form of the IL-2 receptor (sIL-2R), IL-8 and -12 have been suggested, but have not achieved general acceptance as clinical tests. Other biochemical tests that should be performed include full blood count, liver function tests, serum electrolytes and calcium to identify any systemic derangement and specific organ involvement (256). Checking the serum calcium for hypercalcaemia is essential, and hypercalciuria is found in many patients.

2) Biopsy

The diagnosis of sarcoidosis is best supported by the finding of non-caseating granulomas on tissue biopsy, together with compatible clinical and radiological evidence, and with exclusion of other differential diagnoses. Some clinical centres have recommended that the diagnosis of sarcoidosis can only be made when there is granulomatous inflammation in at least two organs to suggest a multisystem disease. However, histological confirmation is not essential for the second organ (144, 407). The other exception to biopsy is when patients present with Löfgren's syndrome, in which the classical presentation of bilateral hilar lymphadenopathy, polyarthralgia and erythema nodosum makes biopsy unnecessary for diagnosis (408). Biopsy should be performed upon the involved organ that is most readily accessible, such as the skin, peripheral lymph nodes or conjunctiva. When other sites are too difficult to biopsy, a lip biopsy can sometimes be helpful, as the disease commonly affects the minor salivary glands and likewise the conjunctivae. Since the lungs and intra-thoracic lymph nodes are most commonly affected in sarcoidosis, bronchoscopy with endobronchial, transbronchial biopsies or transbronchial needle aspiration (TBNA) is commonly employed and histological evidence of non-caseating granulomas is found in 50-85% of sarcoidosis patients. Endoscopic bronchial ultrasound (EBUS), compared to standard bronchoscopy, has improved this diagnostic yield of TBNA to almost 90% and minimised the need for the more invasive mediastinoscopy which is associated with significant cost and morbidity (409–411). CT and nuclear medicine scans can guide the choice of biopsy site which improves the diagnostic yield.

3) Pulmonary Function tests

Two-thirds of patients have airflow limitation at clinical presentation. It is important, therefore, to measure initial lung impairment with pulmonary function tests and to provide a baseline to assess for clinical improvement or worsening of pulmonary disease, as is a chest radiograph, in all patients with suspected sarcoidosis (1). Abnormal pulmonary function tests occur in ~20% of patients with radiographic Stage I disease, compared with 40-70% of patients with Stage II, III or IV disease. Both obstructive and restrictive pulmonary function tests abnormalities may be identified, with common parameters indicating functional impairment being the FVC and diffusion capacity (1, 50, 412), although these tend to return to normal in most patients within 2 years (301).

Airway hyper-responsiveness is common in sarcoidosis (305, 413) and if this is evident then serial pulmonary function testing should always be performed post bronchodilator. It is not clear how much exercise testing adds to the

understanding of functional limitation in sarcoidosis but dyspnoea and exercise intolerance are both common and do not correlate well with resting pulmonary function measures (414). The 6 minute walk test is a well validated field test and correlates with other measurements of respiratory impairment in sarcoidosis (415), but it is not a maximal exercise test. The modified shuttle test approximates peak exercise achieved with treadmill or bicycle and may be suitable for younger patients with minimal pulmonary involvement. Peak VO_2 achieved during a cardiopulmonary exercise test correlates well with modified shuttle walk test distance and the latter test can be performed in the clinic setting (416). Patients with sarcoidosis often experience fatigue and may report muscle weakness in which case handgrip strength and static mouth pressures should be considered, acknowledging high intra-subject variability in both tests (417,418).

4) Radiological Investigations

a) Chest radiography and radiological staging

The chest radiograph remains a common route by which sarcoidosis is suspected or diagnosed. Often, bilateral hilar lymphadenopathy is found in an asymptomatic person who had this investigation for other purposes, e.g. migration. Later stages of disease are often associated with symptoms and are classified according to the system of Scadding as described earlier in this article, with the addition of a Stage 0 representing (418) a normal chest x-ray (394). The chest x-ray can be a useful method for detecting disease regression or progression, but there is as of yet no consensus on whether low dose HRCT can be used as a more sensitive modality to determine treatment responsiveness or spontaneous regression of parenchymal disease (419). Chest CT is an extremely useful diagnostic modality and in the appropriate clinical setting, the appearance of hilar and mediastinal lymphadenopathy combined with the classic parenchymal findings of nodules clustered along the bronchovascular bundles, interlobular septa and subpleurally is considered sufficient to secure the diagnosis without biopsy in some publications (420).

Typically, the disease will affect the right paratracheal, right hilar and left hilar lymph nodes (sometimes called the 1-2-3 pattern), occasionally also causing enlargement of the aortopulmonary window lymph node (1-2-3-4 pattern). Other enlarged lymph nodes may be seen. Lymph nodes may show dense or eggshell calcification. Nodules are the most common of the parenchymal changes being found in nearly all patients varying from a few in a subpleural distribution to profuse micronodules in a primarily upper lobe distribution (421,422). The nodules can be in a patchy distribution, or can cluster and form a 'string of pearls' along the bronchovascular bundles and septa. The nodules can coalesce to form large nodules and masses. Occasionally, small nodules can surround larger lesions, the 'galaxy sign'. Ground glass opacification is thought to possibly represent profuse small nodules beyond the resolution of the high resolution (HR) CT. In many patients with Stage 2 and 3 disease, resolution of the nodules and ground glass changes may occur. Reticular opacities may become apparent in a minority, and often have an upper lobe distribution. Honeycombing may appear.

If the disease progresses to fibrosis, patchy reticular changes and dense opacification become more evident, typically in an upper zone peri-hilar distribution, extending to the apices. Eventually, the distortion results in traction bronchiectasis and if cavity formation ensues then the signs of aspergillomata may be present. Mosaicism representing air trapping is very common on expiratory CT. Bronchial abnormalities are relatively common, with nodular wall thickening and sometimes endobronchial lesions which can occlude small bronchi or local lymph nodes can compress the airways. Small airway obstruction by active disease or by fibrosis can lead to a mosaic pattern associated with gas trapping seen on expiratory views.

The pattern of parenchymal disease on chest CT does correlate with the results of pulmonary function tests and the reticular pattern is most strongly associated with airways disease (423,424). There is no consensus on the value of CT in the follow up of patients with sarcoidosis. The change in extent of disease on CT correlates moderately with change in pulmonary function test variables over time, and this is a stronger relationship than with plain chest radiograph (425). It may well be that a recently described integrated functional and morphologic staging system for sarcoidosis will enable more confident assessment of treatment response (426). Cardiac enlargement can be seen on CT chest scans, suggesting cardiac sarcoidosis, and pulmonary hypertension (PH) may be recognised by right ventricular hypertrophy or enlargement of the pulmonary outflow tract, when compared with the ascending aorta but should be confirmed by echocardiogram and right heart catheterisation if considering specific PH therapy.

b) Nuclear imaging

For many years gallium-67 (^{67}Ga) scintigraphy has been used to identify the classic features of sarcoidosis, the presence of disease suitable for a confirmatory biopsy and to assess involvement of particular organs (335). The classic appearance, particularly in early disease, is that of the panda-lambda sign. The involvement of the salivary glands, conjunctivae and the nasal passages create the impression of the facial characteristics of a panda, while mediastinal and hilar lymph nodes represent the Greek letter lambda. Few other diseases give this appearance. More recently and associated with some difficulties in the supply of ^{67}Ga, positron emission tomography fluorine-18 (F-18) fluorodeoxyglucose (^{18}F-FDG PET) scanning has been shown to be effective in identifying disease that can be sarcoidosis. Neither technique is diagnostic and both rely on pattern recognition. It is evident that ^{18}F-FDGPET will replace ^{67}Ga scanning, given the greater availability of ^{18}F-FDG, as it is also used extensively in oncology and has the advantage of a lower radiation dose, and the ability to co-register the scans with CT imaging (427). Currently it is not reimbursed by the Australian Medicare Benefits Schedule for this indication.

c) Bronchoscopy, BAL and EBUS

Fibre-optic bronchoscopy and bronchoalveolar lavage (BAL) are useful clinical investigations for the pathological diagnosis of sarcoidosis and exclusion of other pulmonary diseases. Bronchoscopy may identify significant laryngeal, tracheal or endobronchial disease with a "cobblestoning" appearance of mucosal granulomatous nodules. Bronchoscopy with transbronchial biopsy has a diagnostic yield of 70–85% and is useful in patients with hilar lymphadenopathy alone based on chest x-rays with Scadding Stage 1 (279, 428). Bronchoscopy allows for TBNA, transbronchial lung biopsy (TBB) and endobronchial biopsy. Endobronchial biopsy may demonstrate non-caseating granulomas even when no endobronchial disease is apparent, and is easy to perform. TBB has the advantage of having a higher rate of obtaining characteristic non-caseating granulomas, at the risk of bleeding and pneumothorax (409, 428).

BAL fluid analysis is a useful investigation for the diagnosis of pulmonary sarcoidosis: detecting a lymphocytosis with elevated ratios of CD4+/CD8+ cells, that are typically >3.5:1, in the absence of other causes (24). BAL lymphocytosis with elevated CD4/CD8 ratios, normal percentages of eosinophils and neutrophils and the absence of plasma cells suggest a diagnosis of sarcoidosis. Cellular analysis of T-lymphocyte subsets and cytokine levels from BAL fluid and peripheral blood using flow cytometry have been compared and can provide useful diagnostic information to identify sarcoid alveolitis. BAL CD4/CD8 ratios greater than 3.5 have a sensitivity of 53%, specificity of 94%, positive predictive value of 76% and a negative predictive value of 85% for sarcoidosis, and with higher ratios the specificity nearly reaches 100% (429). For individual cases, CD4/CD8 ratios may not always be useful and rare cases may present with a CD8 alveolitis, such as in sarcoid patients with HIV-1 infection (430). Increased levels of BAL fluid neutrophils and mast cells have been associated with a worse prognosis (431, 432).

Ex vivo studies of patients with sarcoidosis identified greater activation of non-stimulated BAL CD4+ and CD8+ T cells when compared with peripheral blood lymphocytes (433), demonstrating compartmentalisation of the immune response. Many BAL lymphocytes from patients with active sarcoidosis express cell surface activation markers including CD26, CD54, CD69, CD95 and HLA-DR (433, 434). The number of CD4+/HLA-DR$^+$ cells may be useful for evaluating the activation state of the IL-2 system and defining different phases of sarcoidosis, as numbers decrease in inactive disease (435). BAL fluid from sarcoidosis patients who have the HLA-DRB1*0301-positive genotype predominantly express the Vα2.3 (AV2S3+) T-cell receptor. The increase in AV2S3+ CD4+ T-cells may constitute more than 30% of BAL T-cells, as well as expressing cell surface activation markers including CD26, CD28, CD69 and HLA-DR (122), indicating acute clonal expansion and proliferation in response to inciting antigen(s). A T_H1 CD4+ T-cell alveolitis with elevated ratios of CD4+/CD8+ T-cells has also been confirmed in patients with active pulmonary disease using induced sputum, a relatively less-invasive technique compared with BAL (436).

The high diagnostic yield of EBUS guided fine needle aspiration of intrathoracic lymph nodes makes the use of open surgical lung biopsies, mediastinoscopy and video-assisted thoracoscopic lung biopsy unnecessary in many cases (410). EBUS-TBNA allows real-time ultrasound localisation and aspiration of hilar and mediastinal lymph nodes. It has established itself as an important new technique for the diagnosis of enlarged lymph nodes due to sarcoidosis, with recent evidence of its superiority over conventional 19-gauge needle TBNA in the diagnosis of pulmonary sarcoidosis (409). It is also useful in patients with other intrathoracic lesions who remain undiagnosed despite bronchoscopy and

CT-guided fine-needle aspiration biopsy. Cohort studies of patients with radiological Stage I disease, Stage II disease and those with a high pre-test probability of sarcoidosis (>90%) demonstrate sensitivities between 85–93% (410, 411, 437–440). This minimally invasive procedure can provide a diagnosis in previously challenging cases, without exposing the patient to the risk of complications from more invasive procedures (440,441). EBUS is becoming more frequently used but this approach versus bronchoscopy with TBB will depend on the lesions (e.g. only lymphadenopathy versus mainly lung parenchymal disease) and whether EBUS is available locally. EBUS aspirates of lymph nodes do not always show cohesive granulomas. It would seem prudent to obtain as much information as possible from a bronchoscopy to support a diagnosis of sarcoidosis, particularly if treatment is anticipated. In practical terms, that may mean an EBUS TBNA first if available, followed by BAL and endo- or transbronchial biopsy if the cytologist present at the procedure is unable to see granulomas on the TBNA. Anecdotally, granulomas may be detected on endo-and TBB even if the radiology is normal, which is not unexpected.

d) MRI

i) Imaging for neurosarcoidosis

MRI with gadolinium is superior to CT in terms of detecting neurosarcoidosis. The brain parenchyma is most commonly involved, but pachymeningeal, leptomeningeal and cranial nerve involvement are not uncommon, while skull vault and pituitary lesions are occasionally seen.

ii) Cardiac MRI (CMR)

In general, all patients with parenchymal disease (more involvement than Löfgren's syndrome) should have a baseline ECG and perhaps transthoracic echocardiography, although there is little evidence that the latter is a sensitive screening tool, and of course cannot reliably demonstrate dysrhythmias which are a significant issue with cardiac sarcoidosis. Thus, an ECG indicating unexplained bundle branch block, second or greater degree heart block or ventricular ectopics, should prompt ambulatory ECG monitoring and evaluation for coronary artery disease in the older age groups, and if this is absent a search for cardiac sarcoid by CMR or ^{18}F-FDG PET, or rest/stress sestamibi/^{201}-thallium scan plus ^{67}-gallium depending on local availability. ^{18}F-FDG PET will replace gallium scanning in the next few years. These imaging techniques need to demonstrate both active inflammation and dysfunction, plus exclude coronary artery disease, which usually requires two investigations.

The respective role of these new imaging tools in the diagnostic approach remains to be defined, with some suggestion that CMR may be more sensitive in detecting cardiac involvement than ^{18}F-FDG PET, although specialists in PET have devised specific protocols which offer more specificity than standard oncology ^{18}F-FDG PET scans and perhaps CMR (442, 443). CMR has the advantage of not exposing patients to radiation, but it is not always feasible in those with indwelling cardiac devices.

Cardiac investigations need to be able to identify not just an abnormal area of cardiac tissue (which might be due to ischaemia, for example), but also the presence of inflammation. Hence, an initial technetium scan showing decreased myocardial function may then be followed by CMR confirming an abnormal signal. Special protocols with ^{18}F-FDG PET can detect abnormal uptake in areas of inflammation in the cardiac tissue, but not usually in oncology-related ^{18}F-FDG PET protocols as glucose is avidly taken up by the normal cardiac muscle. A practical guide to the approach is suggested in Mantini et al, with the decision for PET versus CMR being made by local availability (444, 445), but if a dedicated protocol ^{18}F-FDG PET is available, this may be superior (442, 443).

e) Patient Reported Outcomes (see Psychosocial Effects of Sarcoidosis above)

The Fatigue Assessment Score (FAS) and (388–392) two sarcoid specific quality of life instruments can be used to assess patient reported outcomes (393–396) (see above)

5) Further investigations

In patients who present with non-respiratory disease, nuclear medicine scanning may identify other lesions that may be suitable for biopsy, e.g. lymph nodes. Salivary/lip and conjunctival biopsies have been used to identify non-caseating granulomas, as can tissue from skin lesions. The investigations will be generally guided by symptoms and signs, but nuclear medicine has the advantage of being able to assess the whole body and identify areas that are likely to yield a diagnostic biopsy.

NATURAL HISTORY

1) Influence of ethnic and genetic factors

The disease course and prognosis of sarcoidosis vary with ethnicity and genetics. Compared to Caucasians who are likely to present with asymptomatic sarcoidosis, African-Americans tend to experience the more severe form of sarcoidosis and commonly present with extra-pulmonary involvements such as chronic uveitis, lupus pernio, and other cutaneous manifestations. African-American patients are also more likely to have a worse long-term prognosis and higher rates of disease relapse (1). Similarly, the presentation of erythema nodosum, which is often associated with a better disease prognosis, is very rare among African-Americans, although it has been reported in 30% of British and 18% of Finnish patients (446). Japanese patients also have a very low incidence of erythema nodosum and their sarcoidosis-related mortality is mainly from myocardial complications, unlike respiratory failure in other parts of the world (447).

2) Clinical factors of prognostic significance

Sarcoidosis with an acute onset, for example Löfgren's syndrome, has the best prognosis. The manifestation of erythema nodosum is also often associated with a better prognosis as it has a high rate of spontaneous remission at 80%, usually within 6 weeks (448). With prolonged duration of sarcoidosis, the percentage of severe extra-pulmonary manifestations with permanent complications, such as in the heart, liver and central nervous system, increases from only 4-7% of patients at initial presentation to about 10-20%. Only a minority (1-5%) of patients will die from sarcoidosis and the most common causes of death are respiratory failure and neurological or cardiac complications (447). Adverse prognostic factors include age of disease onset greater than 40 years old, manifestations of chronic uveitis, lupus pernio, chronic hypercalcaemia (with or without nephrocalcinosis), respiratory insufficiency and neurological or myocardial involvement (1).

3) Influence of chest radiographic stage

The four chest radiographic (CXR) stages of pulmonary sarcoidosis provide useful prognostic information. Stage I disease has the highest rate of spontaneous remission at 55-90%, compared to 40-70% for Stage II, 10-30% for Stage III and 0-5% for Stage IV (449–451). These remissions usually occur 1-3 years after disease onset (450). American and Japanese patients were reported to have similar resolution rates of their chest radiographic stages of sarcoidosis (301, 452). In contrast to Stage I sarcoidosis, significant morbidity and mortality may result in patients with Stage II-IV disease who have chronic lung parenchymal infiltrates (1). Prospective prognostic studies are less well described in the CT literature as the scanner algorithms and techniques continue to evolve. The CXR is less sensitive in detecting abnormalities that are seen on high-resolution CT scans, and the traditional Scadding stages are less or not applicable to CT scans. Thus, the CT results may imply that patients could have a different CXR stage if lung parenchymal involvement is detected, usually upgrading to a more advanced stage, but whether this is applicable to prognosis is unclear as such prospective studies have not been performed.

4) Biomarkers for monitoring disease course

Various biomarkers, mostly in the serum and BAL of sarcoidosis patients, have been proposed as indicators of disease severity. Some serum markers include ACE, soluble IL-2 receptor, lysozyme and neopterin, while examples of markers in BAL are TNF-α, IFN-γ, collagen III peptide and fibronectin (53). None of these except serum ACE is currently routinely assessed by clinicians. Serum ACE may have a greater prognostic than diagnostic value since in some studies only 40% of patients with clinically active disease have initial elevations in serum ACE (203). The initial serum ACE levels were not significantly different between patients with disease improvement and deterioration, and hence this does not correlate with disease severity. Conversely, the subsequent trend in serum ACE levels after treatment initiation may be helpful in monitoring the efficacy of drug therapy (53), although some studies have reported that corticosteroid therapy has a variable effect on ACE levels, particularly once within the normal range (453, 454).

Soluble IL-2 receptor (sIL-2R), a T cell receptor for IL-2, may be a marker of disease activity because levels significantly increase during active sarcoidosis (455, 456) and decrease during disease remission and during initiation of treatment (457). Lysozyme, which is an enzyme produced by macrophages in sarcoid granulomas, was also found to be elevated in active sarcoidosis (458). Neopterin, produced by activated macrophages, was detected at higher levels in the serum and urine of sarcoidosis patients (459) and at lower levels when the disease resolved (460). Interestingly, progressive disease may be associated with a simultaneous increase in both sIL-2R and neopterin (461). Although the role of chitotriosidase in sarcoidosis remains unknown, serum and BAL levels of this alveolar macrophage enzyme generally increase with disease progression and decrease with treatment (462). Other potential biomarkers include cytokines (TNF-α, TGF-β) (463, 464) and chemokines (CXCR3 ligands, CCL2, CCL5, CCL16, CCL18) (465–469). At present these proposed biomarkers have limited clinical use as diagnostic or prognostic markers due to a lack of conclusive results for their sensitivity and specificity in sarcoidosis.

5) Patient surveillance

There are no data on which to guide surveillance but the 1999 ATS/ERS/WASOG statement makes several reasonable suggestions. Three to six monthly assessments are recommended in the first 2 years, but more frequently in active disease or if treatment has been prescribed. Stage I disease can be monitored less frequently than Stages II-IV. All patients should be monitored for a minimum of 3 and perhaps 5 years after a change in status or the end of treatment. It is likely that Stages II-IV should be monitored indefinitely, but those requiring immunosuppression should be monitored carefully and more frequently, due to the higher likelihood of relapse or complications. Whether those with stable 'burnt-out disease' need lifelong monitoring is less clear, but they are at risk of respiratory failure if their disease is severe and as their lung function declines further with age from the lung function regression equations. While there may be no obvious progression radiographically, airway obstruction and pulmonary hypertension may supervene, which can be monitored by lung function and gas diffusion.

The usual methods of follow-up are: ACE level, serum calcium, liver function tests, lung function tests including diffusing capacity and periodic radiology. An annual ophthalmological review is advisable in the first few years of the disease and at least a baseline ECG. Ectopic beats, any conduction disorder (including partial bundle branch block or first degree block) or episodes of giddiness or syncope should prompt a cardiology review with 24 hr ECG monitoring, echocardiogram and/or a possible cardiac PET or MRI (1).

6) Complications of Sarcoidosis

a) Endobronchial sarcoidosis

Airway obstruction has been noted, and for this reason bronchodilators and inhaled corticosteroids (ICS) are frequently prescribed. However, there is little evidence that ICS is of benefit in this situation albeit these drugs may have an effect on cough (470–472). Endobronchial stenting might be applicable to isolated airway stenoses.

b) Lung fibrosis, fungal infections and aspergillomas

Lung fibrosis with attendant traction bronchiectasis is a common feature of Stage IV disease. Bronchiectasis often develops and may require physiotherapy and treatment of exacerbations with appropriate antibiotics. Often the bronchiectasis is in the upper lobes, associated with the principal site of the disease and therefore may be free-draining but other lobes can be affected.

Intrapulmonary scars and cavities may be complicated by aspergillomas. Aspergillomas can be asymptomatic or present with haemorrhage. The treatment does not differ from other situations with an aspergilloma, with no clear evidence for the appropriate pathway. If treated, patients are usually given antifungals such as itraconazole, voriconazole or posaconazole for months to years, but this is not based on clinical trials. Monitoring of liver function is required if this treatment is initiated. Haemorrhage is best treated by supportive measures and, if more severe, with bronchial artery embolisation. Surgical resection of the aspergilloma is usually reserved for severe and resistant cases and only for selected patients who have sufficient lung function reserve and no other contraindication. Those who are immunosuppressed will have additional risks with surgery. Similarly, patients with sarcoidosis may be at greater risk for other fungal and other diseases due to both scarring, anergy and immunosuppression. Infections such as nocardiosis, pneumocystis and cryptococcosis may need to be considered.

c) Pulmonary Hypertension

This complication is uncommon (5% in specialist referral centres) (308), but increases with the chronicity of the disease and the lung fibrosis. It can rarely be due to a sarcoid granulomatous vasculitis, with sarcoid granulomas in the walls of the pulmonary arteries (WHO Group I), left ventricular failure (Group II) or most commonly, hypoxemic lung disease with fibrosis (Group III). It is most probably under-recognised. It can, however, occur in the absence of major changes in the lung and be manifest as unexplained breathlessness or a decrease in diffusing capacity.

d) Hypercalcaemia

Hypercalcaemia is common in sarcoidosis. It is a treatable cause of acute renal failure in sarcoidosis and hence it is important not to miss this complication (473). It is usually responsive to steroids and rehydration. It is more common in summer than in winter because of the effect of UV light exposure on the skin, increasing vitamin D levels and calcium absorption. It can be useful to enquire about calcium and vitamin supplements and to stop these if they are in use. Protection from sunlight is advisable. Zoledronate may be an alternative therapy if there is a contra-indication to corticosteroids or there is no other disease, but there is only anecdotal evidence.

e) Chronic fatigue

Symptoms may persist after treatment and resolution of sarcoidosis, manifesting as lethargy, depression and chronic fatigue (296, 388, 474) and can be assessed using Patient Reported Outcomes (see above).

f) Mortality

Mortality is rare in sarcoidosis and in non-specialist centres a mortality of less than 1% is quoted (450). Referral bias means that the mortality is over-estimated from specialist centres, and few such estimates include Stage 0 or Stage 1 disease as these are unlikely to be referred. There are regional, ethnic and genetic differences in the types and severity of the disease, but in general, an overall mortality of less than 5% is quoted for those with lung disease. Progressive lung disease, neurological or cardiac involvement increases the risk of mortality.

MANAGEMENT OF SARCOIDOSIS

1) Indications for treatment

In the first instance, patients need appropriate information, and much of the information on the internet applies to those with severe and chronic disease. The majority can be reassured that they have a good prognosis. Useful patient information sheets are available (e.g. http://lungfoundation.com.au/wp-content/uploads/2013/12/Sarcoidosis.pdf, www.europeanlung.org/assets/files/en/publications/sarcoidosis-en.pdf).

The treatment of sarcoidosis is not standardised. The decision to treat is guided by the aim to improve the patient's symptoms and quality of life and to prevent organ damage and complications. One of the treatment criteria is the presence of granulomatous inflammation as evidence of active sarcoidosis since current treatment targets the active inflammatory sites (475). Other considerations include severity of symptoms and disability, the organ(s) involved and related functional consequences if untreated, and whether the likely benefits outweigh the risks of systemic treatment (476).

As a general rule, patients with asymptomatic sarcoidosis should not be treated. Specifically, asymptomatic involvement of the lungs, liver, spleen, bone, intra-thoracic and intra-abdominal lymph nodes rarely requires treatment. As there is minimal physiologic impairment, these patients have an excellent prognosis without development of symptoms or significant organ damage. It is important to monitor these patients carefully in case of possible disease progression, from nodular inflammatory pulmonary disease to irreversible pulmonary fibrosis (477, 478). Sarcoid uveitis must be treated as it may lead to permanent loss of vision (479). Asymptomatic sarcoid calcium derangement also requires treatment to prevent progression to nephrolithiasis and renal insufficiency (480). The treatment of asymptomatic cardiac sarcoidosis and neurosarcoidosis presently remains contentious due to a lack of supporting evidence. However, a group of American clinicians has recommended the evaluation of patients on an individual basis with decision to treat based on positive clinical findings such as "malignant arrhythmias" and change in size of neurological lesions (475).

2) Corticosteroids (CS)

Since the 1950s, systemic corticosteroids have been the mainstay of treatment for both acute and chronic sarcoidosis, but there are no trials to indicate the appropriate dose or duration. It remains the first-line therapy for most forms of the disease (481). The anti-inflammatory action of CS lies in the inhibition of certain inflammatory mediators, particularly IFN-γ and TNF-α, which are key cytokines in promoting sarcoid granuloma formation (106, 476). CS are substituted with other CS-sparing drugs when chronic administration is required or significant side effects have developed. It is important to note that CS and other immunosuppressive drugs only act to suppress, and not cure sarcoidosis, as relapses are frequent once patients are weaned off the drugs (482). The 1999 ATS/ERS/WASOG statement, provided a list of criteria for the initiation of CS therapy in sarcoidosis (Table 3) (1).

Most opinions recommend an initial dose of 20-40mg of prednisolone (1) but these are not based on clinical trials. The Australian Therapeutic Guideline recommends a daily dose of 0.5mg/kg/day of oral prednisolone for 4 weeks, with subsequent tapering or increase, according to clinical and radiological response in individual patients (20). The dose is usually tapered over the course, by 5-10mg every 2-4 weeks down to 7.5-10 mg and then more slowly thereafter, e.g. 1 mg per month. Response is monitored by symptoms and lung function and while radiological changes are useful, they are less able to be repeated frequently. Those who relapse after ceasing treatment will often need a more protracted course, and if a response is observed by 3 months, then to continue for at least 12 months (1). Pulmonary sarcoidosis can be very responsive to systemic CS therapy, unlike neurosarcoidosis, which has only relative responsiveness (475). In some cases of cutaneous and ocular sarcoidosis, topical treatment such as steroid-containing cream or eye drops and intra-lesional or intra-ocular CS injections may be used. Inhaled CS may be sufficient to control cough in patients with pulmonary sarcoidosis; however, its routine use is not recommended, because a meta-analysis did not clearly show a benefit (483). Due to the wide range of side effects that can be caused by systemic CS, patients on chronic CS therapy should receive regular monitoring of their weight, blood pressure, serum glucose, lipids, ophthalmologic examination for glaucoma or

cataracts and bone mineral density, (484). They need to be considered for bone protection, e.g. bisphosphonates, but increased vigilance should occur if calcium and vitamin D are prescribed.

Despite over 60 years of use, there is still insufficient study on the optimal dose and duration of CS treatment and inadequate evidence to prove its long-term benefits (485). The BTS study suggested that a period of observation could be useful, as some improved during the first six months, and CS usage showed only a very modest improvement in spirometry (35). Larger scale studies are needed to establish any longer-term benefits of CS. As such, therapy often needs to be individualised for sarcoid patients. Furthermore, no study to date has clearly proved that CS therapy prevents disease progression or fibrosis development (144). There have also been reports on the development of CS 'resistance' in sarcoid patients as the patients' alveolar macrophages developed enhanced TNF-α production compared with patients who are CS-sensitive (486). Observational studies suggest that severe disease is identified early and leads to earlier CS treatment, and is associated with more frequent relapses (487). From the perspective of this review, pulmonary function tests are the main indicator of response or stability, while serum ACE, calcium, and radiology may be helpful, depending on the presentation. If the disease progresses despite CS, or relapses when the dose is reduced, other treatment options may need to be considered. Usually, the prednisolone dose would be increased in the presence of a relapse, but the addition of another drug may be considered, e.g. azathioprine, methotrexate or a switch to mycophenolate. There are anecdotal reports of non-steroidal anti-inflammatory drugs being useful in Löfgren's syndrome for relief of arthralgia and myalgia.

3) Immunosuppressive Agents

Several immunosuppressive drugs (ID) are used as corticosteroid-sparing agents in patients who require long-term systemic corticosteroid treatment or experience significant steroid-related side effects. This allows the tapering of chronic corticosteroids to its lowest effective dose to minimise adverse drug effects. As most ID take several months to exert their maximal therapeutic effect, corticosteroids should only be tapered after at least 1 month from starting a second agent (475). These drugs are contraindicated in pregnancy, breastfeeding and for a variable period prior to conception. Some restrictions also apply to males as the effects on spermatogenesis and potential teratogenic effects are unknown, and have yet to be reported. There is the risk of infections and the long-term risk of malignancy when using such drugs, which need to be discussed with the patient. Prophylactic treatment with cotrimoxazole may be considered for *Pneumocystis jiroveci* pneumonia prevention. Table 4 summarises the some important pharmacological therapies used to treat sarcoidosis and levels of evidence associated with those treatments.

Methotrexate

Methotrexate, an inhibitor of folic acid metabolism, is the most widely studied CS-sparing agent for the treatment of sarcoidosis. Although it is effective in treating most forms of sarcoidosis involving the lungs, skin, eyes and neurological system, it is used for musculoskeletal disease and pulmonary sarcoidosis (486) and . A range of 50-70% of sarcoid patients treated with methotrexate responded to the treatment (488) and about 25% of patients treated with both corticosteroids and methotrexate could be weaned off the former (489). Side effects of methotrexate include nausea, malaise, mouth ulcers, leukopenia, hepatotoxicity, pneumonitis and an increased risk of opportunistic infections. It is contraindicated in pregnancy. Concomitant folic acid supplement should be given while patients are on methotrexate (475). Recently, multinational evidence-based WASOG recommendations have been developed for the use of methotrexate in patients with sarcoidosis, integrating systematic literature research and expert opinion from sarcoidosis specialists worldwide (490).

Azathioprine

Azathioprine has a similar response rate of approximately 50-70% as methotrexate in the treatment of sarcoidosis (488). It is first converted to its active metabolite 6-mercaptopurine before acting as a purine analogue to inhibit purine synthesis, which is essential for lymphocytic cell proliferation. It has a greater inhibitory effect on cell-mediated immunity than humoral immunity. However, a randomised controlled clinical trial has yet to be conducted to evaluate the efficacy of azathioprine for the treatment of sarcoidosis (475). Common side effects reported by patients include rash, fever, malaise and gastrointestinal disturbances. Azathioprine-induced hepatotoxicity may also occur but is reversible with drug withdrawal. Due to its possible teratogenic risk, women of reproductive age must be advised to use contraception during treatment, although this is more of a concern with methotrexate and mycophenolate (488, 491). The risk of

serious adverse effects can be reduced by screening the patient for the thiopurine methyltransferase level, and this should now be measured routinely before prescribing azathioprine.

Mycophenolate

Mycophenolate has been recommended as an effective treatment for neurosarcoidosis (492) and cutaneous sarcoidosis, while data on its efficacy for other forms of sarcoidosis is limited (493). It inhibits purine synthesis which is essential for lymphocytic expansion. The most common side effects are vomiting and diarrhoea, hypercholesterolemia, hyperglycaemia, bone marrow suppression and hepatic enzyme induction. Similar to most cytotoxic drugs, mycophenolate is contraindicated in pregnancy due to its association with congenital defects and spontaneous abortions (475, 492).

Leflunomide

Limited studies have suggested that leflunomide, may be as effective as methotrexate in treating both pulmonary and extra-pulmonary sarcoidosis. Compared to methotrexate, it has less hepatotoxicity and pulmonary toxicity, for example, interstitial pneumonitis (494). It may be used as a monotherapy or conjunct therapy, depending on the disease severity (495). It exerts its immunosuppressive activity by inhibiting de novo pyrimidine synthesis, via the mitochondrial enzyme dihydro-orotate dehydrogenase (DHODH), essential for synthesis of uridine monophosphate (rUMP) synthesis, which is necessary for lymphocyte proliferation (496). Due to its long half-life of 14-15 days and relatively longer time to achieve steady state levels, significant leflunomide toxicity may occur. This can be reversed with cholestyramine, which increases rate of drug elimination. Some of the most frequently reported side effects are diarrhoea, hypertension, rash, alopecia, peripheral neuropathy, arthralgia and blurred vision. Leflunomide is also contraindicated in pregnancy (497). It may persist in the body for years. Plasma levels are now available and should be performed prior to conception and record <0.02 mg/L at least twice, 2 weeks apart.

Cyclophosphamide

Due to the risk of severe toxicity, cyclophosphamide is usually reserved for treating sarcoidosis that has become refractory to CS and other corticosteroid-sparing agents, particularly life-threatening neurosarcoidosis (498) and cardiac sarcoidosis (499) but it is rarely used since the advent of TNF inhibitors. Cyclophosphamide is an alkylating agent that cross-links DNA strands and in turn inhibits DNA synthesis, hence interfering with lymphocytic cellular division. The intravenous route of administration may be preferred over the oral route because it results in 50% less cumulative dosing and associated toxicity when studied in other diseases (500). Cyclophosphamide may cause both male and female infertility by interfering with spermatogenesis and oogenesis. Reliable contraception should be used to avoid its teratogenic risk and gamete preservation should be considered in those of reproductive age. Long-term oral cyclophosphamide has also been associated with haemorrhagic cystitis and transitional cell carcinoma of the bladder (501).

4) Tumour Necrosis Factor-α inhibitors and other monoclonal antibodies

Overall, there are some, if modest, beneficial effects of TNF-α inhibitors (e.g. infliximab, adalimumab, certolizumab and golimumab) in the treatment of refractory sarcoidosis. Cost, side effects and their limited effect discourage their use, such that most clinicians would reserve the use of such therapy after failure of CS and other immunosuppressive agents (502). There is some logic to using such agents, because the development of granulomas is thought to be dependent upon TNF-α. The studies to date are limited to a few placebo-controlled trials and several case series and case reports (503–507).

The largest trial was that of infliximab, an anti-TNF-α monoclonal antibody and which was a logical choice (503). The trial showed a very small benefit in terms of lung function, but other trials have been commenced and case series/anecdotal reports suggest some of these agents may be of value. In terms of lung disease, there was a very small improvement in forced vital capacity with infliximab, perhaps more noticeable in those with active, symptomatic Stage IV disease (503). In light of these studies, other non-biological inhibitors of TNF-α have been studied in small, often uncontrolled clinical trials, particularly for lupus pernio in which disease presentation they may be more effective (e.g. pentoxifylline, thalidomide, with its attendant risks in pregnancy) (508). The use of other agents such as anti-CD20 (rituximab) have yet to be studied in a controlled manner (509), but logically, an intervention that targets CD4 cells, or the T_H1 (and perhaps

T_H17) pathways would be of potential benefit. The obvious problems are those of cost and availability to those patients for whom the drugs are not reimbursed or covered by national prescribing programmes. It is important to exclude other diseases that could be activated with TNF-α suppression (e.g. multiple sclerosis, tuberculosis, fungal and viral infections).

5) Other Medications

Some clinicians use non-steroidal anti-inflammatory agents, particularly in those with acute sarcoidosis (e.g. arthritis and Löfgren's syndrome). There appear to be few data to support their use but these may be associated with symptomatic improvement, particularly if an inflammatory arthritis is prominent. It is doubtful that these change the course of the disease. Several other drug modalities have been tried in chronic sarcoidosis, usually in the context of chronic and cutaneous sarcoidosis, such as hydroxychloroquine and anti-tuberculous medication. Again, these are limited to small studies, but often a positive effect has been documented (510). Some reports have included the use of anti-fungal agents, but these have been small studies from a few specific centres.

6) Lung and other Organ Transplantation

Refractory and severe, end-stage pulmonary sarcoidosis is an indication for consideration of lung transplantation and successful cases have been documented. It is thought that the subsequent immunosuppression usually protects the patient from recurrence of the disease, which has nonetheless been described in the donor organ, with aggregates of T lymphocytes from the recipient (166, 511, 512). Other case reports exist of sarcoidosis being transferred to the recipient from the donor lung (166). The transplantation of other organs for sarcoidosis is also well-described, e.g. cardiac.

7) Other organ involvement

Treatment of cardiac sarcoid is based on systemic corticosteroids, cardiac pharmacological agents (513, 514), and the placement of a pacemaker or implantable cardiac defibrillator in case of atrioventricular block, severe ventricular arrhythmias and those with significantly reduced left ventricular ejection fraction. Cardiac transplantation has also been used in cases of advanced infiltrative disease (333). Corticosteroids may improve severe hepatic dysfunction, particularly if there is risk of fibrosis, but hepatic transplantation may be required in severe disease (515).

The use of immunosuppressive agents such as methotrexate, azathioprine, mycophenolate and cyclophosphamide has been advocated (344), and these agents should be considered for the treatment of some manifestations of neurosarcoidosis and as steroid sparing agents (342). Sarcoid disease of the eye is a specialist topic, but can include cycloplegics, topical CS, intralesional injections, depot injections and if these do not control the disease, systemic therapy as described above. (516))

FUTURE DIRECTIONS

Despite advances in our knowledge of sarcoidosis, the exact aetiology and immunopathogenesis of the disease remain ill-defined. Different possible aetiological agents, including microbial, occupational and environmental substances, have been postulated by various studies, but there is still a need for more definitive and conclusive studies to confirm the reproducibility of these findings. Although it is widely accepted that sarcoidosis develops in individuals with a genetic predisposition involving HLA and non-HLA genes, many investigations have failed to identify a genetic "signature" associated with sarcoidosis. However, certain genetic associations with disease subtypes and epidemiological populations have been established. Further research is required to unravel this complex and polygenic interaction responsible for the immunopathogenesis of sarcoidosis, preferably in conjunction with more systemic epidemiological studies. This will help to clarify if sarcoidosis simply involves a direct causal relationship with a specific aetiological agent or if it requires a combination of multiple triggers such as host genetic and environmental factors, and that this in fact is a syndrome brought on by several agents and genetic tendencies.

Our understanding of the disease process is further complicated by the immune paradox in the peripheral blood and sites of sarcoid granulomatous inflammation, which distinguishes sarcoidosis from other diseases. There is therefore a need to further investigate the recently proposed $T_H1/T_H2/T_H17$ paradigm and the exact role of Treg cells and CD28 down-regulation in sarcoid peripheral anergy. Functional cellular studies may provide insights into whether an increased quantity or an altered functional capacity of different immune cells is more significant in causing the disease. Recent technological advances in genomics, proteomics, metabolomics and microbiomics have been promising and can provide more concrete findings to elucidate sarcoid immunopathogenesis at the molecular level. Profiling of gene expression in the blood and other biological fluids at disease onset may also provide new insights into the activity and likely progression of the disease, which will in turn allow identification of patients at risk of developing chronic sarcoidosis and pulmonary fibrosis.

Sarcoidosis may have been under-diagnosed in most clinical circumstances as a result of the heterogeneity of disease manifestation and the lack of sufficiently sensitive and specific diagnostic tests for the different disease subtypes. At present, sarcoidosis is still a diagnosis of exclusion, which requires histological evidence of non-caseating granulomas on tissue biopsy. It would be ideal if the diagnosis could be made by a non-invasive method such as the measurement of certain disease markers in the patient's blood. Although various biomarkers have been proposed for diagnosis and disease monitoring, there is still no single biomarker that can specifically and sensitively differentiate sarcoidosis from other diseases. There is evidence that from the perspective of patients, the use of minimal corticosteroid is probably better and patient-related outcome measures may also inform outcomes in terms of value, quality of life and the prioritisation of sarcoidosis treatment. Further research is necessary to find novel markers that will be useful for future clinical practice. There is also a need to improve the currently available treatments for sarcoidosis and to design new therapies with better efficacy and fewer side effects, especially if long-term treatment is required. Ideally, if the antigens responsible for sarcoidosis could be identified, then prevention might be possible.

Table 1: HLA gene associations in sarcoidosis

HLA gene	Risk Alleles	Association	Reference
HLA-A	A*1, A*	Susceptibility	(102, 108)
HLA-B	B*7, B*8	Susceptibility in many populations	(108, 110, 517, 518)
HLA-DPB1	*0201	No association with sarcoidosis	(519)
HLA-DQB1	*0201	Protection, Löfgren's syndrome, mild disease	(114, 121)
	*0602	Susceptibility/disease progression	(114, 126)
HLA-DRB1	*01	Protection in several populations	(102, 520)
	*0301	Acute onset/good prognosis	(110, 120, 127, 136, 517)
	*04	Protection in several populations; ocular sarcoidosis and Heerfordt's syndrome	(133, 521, 522)
	*11, *14 and *08	Japanese patients	(523)
	*1101	Susceptibility in whites and African Americans	(66)
	*12	Susceptibility	(66, 520)
	*1501	Severe pulmonary sarcoidosis	(120, 126)
HLA-DRB3	*0101	Susceptibility/disease progression	(524)
	*1501	Löfgren's syndrome	(66, 126)

Table 1: Summary of key HLA gene associations identified in sarcoidosis.

Table 2: Non-HLA gene associations in sarcoidosis

Candidate Gene	Chromosome Location	Putative association	Reference
Angiotensin converting enzyme (ACE)	17q23	Increased risk for disease susceptibility with ID and DD genotypes. Moderate association with II genotype and radiographic progression.	(525-528)
ANXA11	10q22.3	Susceptibility of Löfgren's (with protection against disease) and non- Löfgren's disease	(148, 149, 529, 530)
BTNL2	rs2076530 SNP in 6p21	rs2076530 G->A is associated with sarcoidosis in white patients	(105, 128, 130, 131, 531-533)
C-C chemokine receptor 2	3p21.3	Protection/Löfgren's syndrome association	(136, 534-536)
C-C chemokine receptor 5	3p21.3	Association of CCR5Δ32 allele more common in patients needing corticosteroid therapy; association later refuted with haplotype analysis and larger sample size.	(536-538)
CD80, CD86	3q21	No association detected	(539)
Clara cell 10 kD protein	11q 12-13	An allele associated with sarcoidosis and progressive disease at 3 year follow-up	(540)
Complement receptor 1 (CR1)	1q32	The GG genotype for the Pro1827Arg (C (5,507) G) polymorphism was significantly associated with sarcoidosis, association of CR1 polymorphisms refuted in another study.	(541, 542)
Cystic fibrosis transmembrane regulator	7q31.2	R75Q may increase sarcoidosis susceptibility risk	(543, 544)
Fas promoter gene	10q24	Haplotype of the Fas promoter polymorphisms-1377G/-690T/-670G associated with susceptibility in African Americans	(545)
HSPA1L heat shock protein 70 1 like	6p21.3	HSP(+2437)CC associated with susceptibility and Löfgren's syndrome	(546)
Inhibitor κ B-α	14q13	Association with -297T allele. Association of haplotype GTT at -881, -826, -297 respectively. Allele -827T in Stage II pulmonary sarcoidosis	(547)
Interleukin-1α	2q14	The IL-1α -889 1.1 genotype increased risk	(548)
Interleukin-18	11q22	Genotype -607CA increased risk over AA. No association with organ involvement. Association refuted in Dutch patients.	(549-551)
Interferon-γ	9p22	IFNA17 polymorphism (551T->G) and IFNA10 (60A) IFN-α17 (551G) haplotype increased risk.	(135)
Natural resistance associated macrophage protein (NRAMP or SLC11A1)	2q35	Protective effect of (CA)(n) repeat in the immediate 5´ region of the NRAMP1 gene	(552, 553)
Toll-like receptor 4, TLR10-TLR1-TLR6 cluster	9q32	Asp299Gly and Thre399Ile mutations associated with chronic disease. Genetic variation in the TLR10-TLR1-TLR6 cluster associated with increased risk of chronic disease.	(139, 140, 554)
Transforming growth factor (TGF)	19q13.2	TGF-β2 59941 allele, TGF- β3 4875A and 17369 C alleles were associated with chest x-ray detection of pulmonary fibrosis	(555, 556)
Tumour necrosis factor-α (TNF-α)	6p21.3	Genotype -308A variant allele associated with Löfgren's syndrome & erythema nodosum; -857T allele with sarcoidosis. -308A was not associated with sarcoidosis in African Americans	(526, 557-560)
Vascular endothelial growth factor (VEGF)	6p12	Protective effect of +813 CT and TT genotypes; lower FEV_1/FVC ratio observed with -627 GG genotype.	(561)
Vitamin D receptor	12q12-14	B allele elevated in patients with sarcoidosis	(526, 562, 563)

Table 2: Summary of key candidate non-HLA gene associations identified in sarcoidosis.

Table 3: ATS/ERS/WASOG criteria for initiating corticosteroids in sarcoidosis

Progressive symptomatic pulmonary disease
Asymptomatic pulmonary disease with persistent infiltrates or progressive loss of lung function
Cardiac disease
Neurological disease
Eye disease not responding to topical therapy
Symptomatic hypercalcaemia
Other symptomatic/progressive extrapulmonary disease

Table 3: ATS/ERS/WASOG criteria for initiating corticosteroid therapy in patients with sarcoidosis (1).

Diagram (adapted from Ahmadzai H, Wakefield, D., Thomas, P.S. The potential of the immunological markers of sarcoidosis in exhaled breath and peripheral blood as future diagnostic and monitoring techniques. Inflammopharmacology. 2011;19 (2):55-68 and Ianuzzi et al (106) with permission

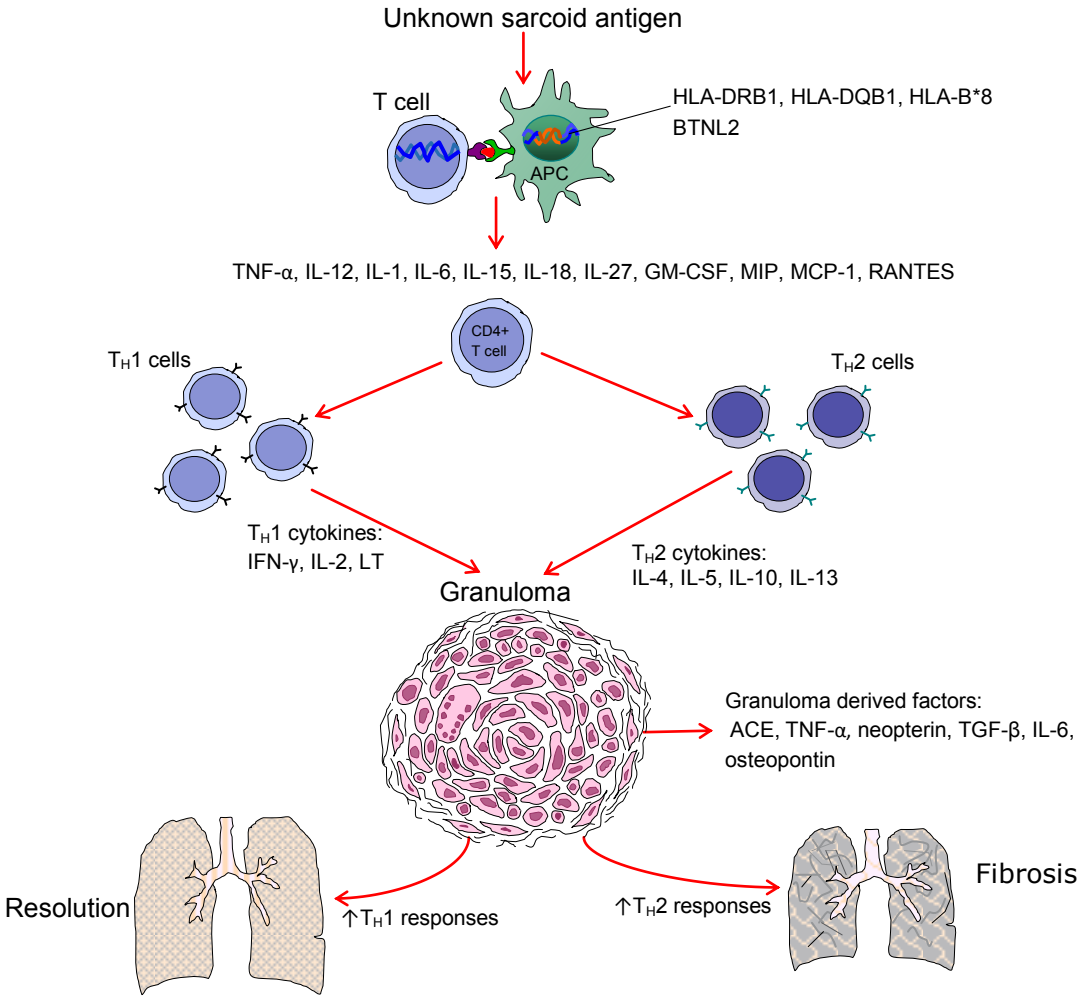

Figure 1: Overview of the hypothesised immunopathogenesis or sarcoidosis. The inciting agent may be cleared leaving behind an undergradable antigen or it may cause a cross-reacting response with a self-antigen with strong evidence for HLA and BTNL2 alleles contributing to susceptibility. The processed antigen is presented by HLA molecules on antigen presenting cells (APC) to 'sarcoid' antigen specific T cells, which express restricted Vα and Vβ regions of the T cell receptor. Ligation of co-stimulatory signals such as CD80 and CD86 on the APC binding to CD28 and CD154 on the T cell is required for full T cell activation. This leads to release of a variety of cytokines and chemokines activating CD4+ T cells to become active $T_{11}1$ cells that secrete IL-2 and IFN-Ч that drives granulomatous inflammation yet promotes resolution. Contribution of $T_{11}2$ cells and macrophage derived cytokines namely TGF-β lead to development of fibrosis and chronic disease. Diagram modified from Ianmuzzi, Rybicki & Teirstein (2007)

Table 4: Pharmacologic treatments for pulmonary sarcoidosis and levels of evidence for each treatment

	Level of evidence	Comment
Inhaled corticosteroids	A	Conflicting results from a small number of trials but essentially ineffective for control of pulmonary disease. May be effective for cough symptom control (471, 564, 565)
Oral corticosteroids (35)	B	No robust placebo controlled RCT
(Hydroxy) chloroquine	B	One small RCT in pulmonary disease. May be useful as a steroid sparing agent (566)
Methotrexate (490)	A	Steroid sparing agent: one small RCT in pulmonary disease and several case series in extra-pulmonary disease (567)
Azathioprine (488)	B	Steroid sparing
Mycophenolate (492, 493)	C	Steroid sparing
Leflunomide (494, 495)	B	Steroid sparing
Infliximab (503)	A	One RCT demonstrating small effect in pulmonary disease, underpowered to demonstrate effect on extra-pulmonary manifestations
Adalimumab	B	One small RCT in skin disease. Case series in pulmonary disease. Lower rates of immunogenicity and allergy symptoms (505, 568, 569)

Level A: At least one double-blind, placebo-controlled trial with positive results with one or more case series supporting the results. Level B: Majority of case series showing positive results. Level C: Case series with mixed reports of effectiveness, or only a small number of cases reported. Scoring level of evidence as proposed by Guyatt G et al (570).

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