Sarcoidosis

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There have been several new insights into the cause and treatment of sarcoidosis. Studies of genetic variation have shown that specific genetic polymorphisms are associated with increased risk of disease or affect disease presentation. These polymorphisms include variation of MHC and cytokines such as tumour necrosis factor (TNF). Not all investigators have come to the same conclusion, suggesting an interaction of various factors, including the patient’s ethnic origin. Treatment of sarcoidosis varies considerably. Patients with symptomatic disease for more than 2–5 years have been of particular interest. Corticosteroids remain the standard of care in such cases, but immunosuppressive drugs have proved steroid-sparing in many patients. New agents, including pentoxifylline, thalidomide, and infliximab have proved useful in selected cases. The effectiveness of these agents seems to lie in their ability to block TNF, especially in the treatment of chronic disease.

Over 100 years since the first clinical description of sarcoidosis, we still do not know the cause of this multiorgan disease. Some investigators have provided insight into the genetic risks for sarcoidosis and how the genetic makeup of a patient (genotype) determines the clinical presentation and outcome (phenotype) of an individual’s disease. However, the phenotype of sarcoidosis for the chronic patient, who has active symptomatic disease for more than 2 years, clearly needs a different treatment approach to avoid toxicity from long term corticosteroids. The use of new agents for these patients has developed from enhanced knowledge of the role of the cytokines, such as tumour necrosis factor (TNF), in the pathogenesis of sarcoidosis. The blockade of TNF α has already proved effective in treatment of rheumatoid arthritis. We will discuss the role of this new information in the assessment and management of patients with sarcoidosis.

Epidemiology

Sarcoidosis is a granulomatous disorder of unknown cause, affecting multiple organs. The cells of the granuloma are organised spatially as immune granulomas, the hallmark of sarcoidosis, and the result of an immunological response to an antigenic trigger. Although precise epidemiological studies have not been undertaken, there are several reasons why we might infer that an infective agent or agents might be the trigger(s), including spatial, seasonal, and occupational clustering.

An investigation of an outbreak of sarcoidosis on the Isle of Man, UK, noted temporal and spatial associations of sarcoidosis frequency for individuals who lived within 100 metres of each other, during 7 years that included the 5 years before and the 2 years after diagnosis. Other clusters of sarcoidosis have been reported in northern Sweden and in central Hokkaido in Japan. Seasonal clustering has been reported in Greece (70% of cases identified between March and May every year), Spain (almost 50% of diagnoses between April and June) and Japan (diagnosed mostly during June and July). Occupational clustering also occurs. In the USA and the UK, a higher percentage of cases was recorded in health care workers than in the general population. Whether this difference was related to an enhanced likelihood of ascertainment is unclear. Other reports of increased frequency of sarcoidosis have been described in studies of naval aircraft servicemen and fire fighters in the USA. These clusterings of disease in individuals who share environments lend support to the notion that an agent to which they had all been exposed might be the trigger. Results of many studies have suggested putative infective triggering agents but the designs of these studies have never been sufficiently robust to confirm unequivocally that a specific agent is causative. However, two agents have emerged as probable candidates—mycobacteria and propionibacteria.

In at least 19 studies, researchers have explored the role of mycobacteria in triggering sarcoidosis. The robustness of methodology varied considerably between these studies, as did the numbers of individuals studied. Positivity rates have varied greatly between the published studies—from 0% to 89%. The most compelling investigation by Vokurka and others, using PCR methodology that can detect as few as one copy of the genome identified no Mycobacterium tuberculosis DNA in tissue samples obtained from patients with sarcoidosis. With such variability, firm conclusions are difficult to draw but perhaps the most balanced conclusion is that in some patients mycobacteria could be the trigger.

The role of Propionibacterium acnes and P granulosum has been investigated. PCR amplification of biopsied thoracic lymph nodes was used to identify propionibacterial DNA. Strict controls were used for both positivity (tuberculous lymph nodes) and negativity (lymph nodes removed for suspect lung cancer) and the
amount of DNA quantified. Strikingly higher propionibacterial DNA copy numbers were seen in sarcoidosis compared with the other diseases. The possibility that this organism is the trigger is persuasive because the disease largely affects individuals in early adult life following a time in which acne is highly prevalent.

**Genetic susceptibility**

Sarcoidosis is genetically a complex disease whose genetic predisposition is determined by the varying effects of several genes. There are various lines of evidence that would support this idea. First, there is variable prevalence and incidence in severity of the disease in individuals of different races and ethnic backgrounds. Second, there is a higher likelihood of developing sarcoidosis if a first-degree or second-degree family member has sarcoidosis, and this relative risk ranges from 36 to 73 in studies from the UK and USA. Third, Schürmann and others investigated 138 individuals from 63 German families and used microsatellite markers to identify areas of the genome linked to the disease. The most prominent finding was of linkage to a section within MHC on the short arm of chromosome 6. This finding is in keeping with a series of chromosome marker studies of both familial and sporadic cases in which the TNF complex located adjacent to the MHC class II alleles and sarcoidosis, What is emerging from these studies is that there seems to be several alleles that confer susceptibility to disease (HLA DR1, DR4, and possibly HLA DQ*0202). Future work might well show that the severity of disease is also genetically determined.

Genetic studies of complex diseases are not without difficulty, and the inherent issues have been set out elegantly in Silverman and Palmer’s review, in which they discuss linkage disequilibrium. An apparent association between a particular gene and disease might actually be a marker of a much stronger association between an adjacent gene and disease. In this respect, the TNF complex located adjacent to the MHC class II loci on chromosome 6 might play an important part in determining severity of disease, together with MHC class II alleles. The –308 promoter polymorphism of TNF α has proved to be associated with Löfgren’s syndrome, which is the form of sarcoidosis with a good prognosis. Similarly there are other promoter polymorphisms in the TNF gene that could modify the severity of disease in a particular individual.

Genetic associations will therefore need to be examined with the idea in mind of extended haplotypes (a series of genes linked on the same chromosome) to better define issues of susceptibility and severity.

**Other genetic loci of interest**

The MHC class II region of the genome is the most likely target region for identification of disease susceptibility, not only because of the microsatellite marker studies of Schürmann and co-workers, but also because the class II genes determine presentation of antigen to the T cell at the initiation of the response that results in immune granuloma formation. In other words, there is a functional as well as a linkage relevance to investigation of these genes.

Similarly, there are other genes (candidate genes) that have been targeted because of their known expression in disease. One of these, the best studied has been the 267 bp insertion/deletion polymorphism in intron 16 of the angiotensin-converting enzyme (ACE) gene. Several studies have shown no relation between this polymorphism and disease susceptibility, apart from one of African-Americans in Detroit in whom the deletion allele was most frequent in individuals with disease. Other workers have tried to define the role of this polymorphism in disease progression, but their findings are inconclusive. A detailed assessment of clinical resolution of disease over 5 years showed that those homozygous for the deletion were the most likely to have persistent disease, whereas other workers were unable to identify a relation between polymorphism pattern and disease severity. Results of one study of familial disease have suggested that this ACE polymorphism is a cofactor in disease manifestation. Other researchers in candidate gene studies have not yet identified any locus more important than the class II region. The combination of more high-resolution chromosomal marker studies of both familial and sporadic cases and the identification of potentially key candidates in the regions identified, will probably yield clearer answers about quantification of genetic predisposition conferred by different genes to disease susceptibility and severity.

**Immunological response**

There are two aspects of the granulomatous response of sarcoidosis—the initial event leading to granuloma formation, and the evolution of the response as either resolution or chronic disease. Figure 1 summarises what is known or suggested about this inflammatory response. The exact point when sarcoidosis starts is usually unclear. An exception may be Löfgren’s syndrome of erythema nodosum, hilar adenopathy, and associated uveitis. Patients are generally symptomatic from the
erythema nodosum and associated arthralgias, and seek medical attention. In studies of patients with this very acute form of the disease, a high proportion of CD4-positive lymphocytes have been identified in bronchoalveolar lavage (BAL) fluid.51 These T cells are activated, as shown by their increase of interleukin (IL) 2 receptors and the spontaneous release of IL 2 by these cells.51 IL 18 has also been reported as possibly playing a central part in sarcoid granuloma formation. 52 This activation is associated with macrophage activation, interferon production, and formation of the granuloma, and has been cited as an example of the Th-1 response. 53 In more than 60% of sarcoidosis patients, the granulomatous response resolves during the following 2–5 years. The events leading to resolution include an influx of CD-8 positive lymphocytes.54 The maintenance of the granuloma may be through the IL 12, and resolution is associated with the cytokine IL 10, which suppresses the inflammatory response.55 The remaining patients have chronic disease, which can include fibrosis. The cytokines associated with chronic disease include IL 8, IL 12, and TNF.56-58 The persistence of increased release of TNF by alveolar macrophages has proved to lead to more frequent use of long-term therapy.56 IL 8 is not usually seen in the BAL fluid of early disease. In patients with chronic disease, raised IL 8 has been identified. The concentrations were close to those in patients with idiopathic pulmonary fibrosis.56 The increase in IL 8 has been associated with transforming-growth-factor β, a cytokine that promotes fibrosis.

Diagnosis
The pathological finding of sarcoidosis is a granuloma. These granulomas are usually non-necrotising, but occasionally necrosis is seen.57,58 The finding of a granuloma is not specific for sarcoidosis, since many other conditions can cause granulomas.59,60 Among the conditions that can be confused with sarcoidosis are tuberculosis and deep-seated fungal infections, but these usually have frank necrosis. Malignant diseases can also cause a granulomatous reaction, including lymphoma59 as well as epitheloid reaction such as breast and lung cancer.59

In most cases, the clinical presentation of the patient with sarcoidosis is as important as the histopathological information. Although presentations of sarcoidosis can vary enormously, a common feature of the disease is multiorgan involvement, and the clinical likelihood of sarcoidosis will rise when more than one affected organ can be documented. How clinical features can suggest sarcoidosis, leading to diagnostic testing, is shown in figure 2, and some of the common radiographic and cutaneous findings in sarcoidosis in figures 3 and 4. Positive diagnostic testing, such as biopsy, need to be supported by clinical features. This algorithm is a summary of the recent statement on sarcoidosis.60

There are new imaging tests being evaluated in sarcoidosis. The use of CT in the routine assessment of sarcoidosis patients is controversial, since it seems unnecessary and expensive.66 However, there are characteristic findings identified on CT scans that strongly support the diagnosis of sarcoidosis, including the presence of mediastinal and hilar adenopathy, lung disease with upper lobe predominance, peribronchial irregularities, and subpleural micronodules (figure 4).67 None of these findings are specific enough to be thought diagnostic for sarcoidosis. CT scans can assist in the assessment of a patient with possible extrapulmonary sarcoidosis, such as neurological or ocular sarcoidosis, in which the clinician is trying to establish whether to approach the lung for a diagnostic procedure such as mediastinoscopy or bronchoscopy. Magnetic resonance imaging (MRI) can also show evidence of sarcoidosis in a particular organ, including neurological, muscle, and bone disease.68 Contrast enhancement with gadolinium improves the sensitivity of the technique. Positron emission tomography (PET) scanning with various

Figure 2: Summary of the approach to diagnosis of sarcoidosis
Based on the recommendations of an expert panel.69
markers has shown evidence of disease activity in sarcoidosis. Occasionally this technique can be used to detect a possible biopsy site.

Extrapulmonary manifestations of sarcoidosis seem to vary with ethnic origin and sex. Panel 2 shows some of the common differences reported for ethnic group or sex. One limitation of research reports has been the variability of definition of organ involvement by sarcoidosis. A recently proposed system was successful in categorising over 99% of specific organ involvement in a large number of new cases of sarcoidosis.

Treatment

The most satisfying therapy for the patient and physician in sarcoidosis is no treatment at all. For many patients, systemic treatment is not necessary for the disease. Systemic therapy varies between treatment centres, with some groups treating only a third of their patients, and others more than two-thirds. For patients needing systemic therapy, there is a subgroup with chronic disease in whom disease does not resolve after 2–5 years. These chronic patients often need long-term therapy and may require corticosteroids or other treatments for 5 or more years.

The evidence lends support to the use of corticosteroids for patients with symptoms. There are several conditions in which some form of treatment should always be offered to the patient. These include patients with neurological, cardiac, sight-threatening ocular, and serious respiratory involvement, and hypercalcaemia. Fatigue is a common symptom in sarcoidosis and for patients incapacitated in this way, systemic therapy should be considered. Despite the widespread use of corticosteroids in sarcoidosis, there is little evidence of long-term benefit. Several workers have tried to define the role of corticosteroids in sarcoidosis. Results of randomised trials have often failed to show long-term benefit for these drugs. Uncontrolled trials have supported the use of long-term treatment for the symptomatic patient.

Two studies have provided complementary information about the use of corticosteroids in patients with persistent chest radiographic abnormalities, but no serious pulmonary symptoms. Investigators for the British Thoracic Society (BTS) randomised this group of patients to either 18 months of corticosteroids or observation. For the observation group, 20% of the patients progressed and were treated with corticosteroids. 5 years after the treatment period ended, the patients routinely given corticosteroids still had much improved lung function, although the improvement in vital capacity was only 10-4%. In another study of long-term treatment,
Pietinalho and colleagues⁸⁵ compared, in the largest study so far, 3 months of prednisone followed by 15 months of inhaled corticosteroids (budesonide) with placebo. They showed that corticosteroid therapy was of benefit, especially for those with parenchymal disease as seen on chest radiography.⁸⁶ This benefit persisted for 5 years after stopping routine therapy.⁸⁶ The degree of improvement averaged 10%, which is similar to what was seen in the BTS study. Whether the risks associated with long-term corticosteroids are worth the modest benefit seen in these studies of patients without symptoms remains unclear. Much depends on the lung function: in more severe, even asymptomatic disease its seemingly modest improvement could be argued to outweigh the risk of drug side-effect. The use of inhaled corticosteroids is appealing, although these drugs would not benefit extrapulmonary disease. In studies of fluticasone, researchers have not been able to show a steroid-sparing effect for symptomatic patients with acute or chronic disease.⁸⁷,⁸⁸

The conventional steroid-sparing agents for sarcoidosis have included antimalarial and cytotoxic agents. The antimalarial agent chloroquine proved a useful steroid-sparing agent in a randomised trial of chronic pulmonary sarcoidosis patients needing high-dose corticosteroids.⁹⁰ The effect of the drug was modest, but the side-effects of chloroquine were few, although hydroxychloroquine is less oculotoxic than chloroquine.⁹¹ Others have reported that chloroquine and hydroxychloroquine are useful for neurological sarcoidosis⁹¹ and for hypercalcaemia seen with sarcoidosis.⁹² In a retrospective review of the efficacy

### Panel 2: Specific extrapulmonary manifestations associated with sex or ethnic origin

<table>
<thead>
<tr>
<th>Drug</th>
<th>Women</th>
<th>Men</th>
<th>Scandinavian</th>
<th>Italian</th>
<th>Japanese</th>
<th>African-American/West Indies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema nodosum</td>
<td>Yes</td>
<td>..</td>
<td>..</td>
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<tr>
<td>Lupus pernio</td>
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<td>..</td>
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<td>..</td>
<td>Yes</td>
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<tr>
<td>Eye</td>
<td>Yes</td>
<td>..</td>
<td>..</td>
<td>..</td>
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<td>Yes</td>
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<tr>
<td>Cardiac</td>
<td>..</td>
<td>..</td>
<td>..</td>
<td>..</td>
<td>Yes</td>
<td>..</td>
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<tr>
<td>Liver</td>
<td>..</td>
<td>..</td>
<td>..</td>
<td>..</td>
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<td>Yes</td>
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<tr>
<td>Bone marrow</td>
<td>..</td>
<td>..</td>
<td>..</td>
<td>..</td>
<td>..</td>
<td>Yes</td>
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<tr>
<td>Hypercalcaemia</td>
<td>..</td>
<td>Yes</td>
<td>..</td>
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</table>

### Panel 3: Commonly used drugs for sarcoidosis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual dose</th>
<th>Common toxicities</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td>Initial: 20–40 mg daily; Maintenance: 5–10 mg daily or every other day</td>
<td>Diabetes, hypertension, osteoporosis, insomnia, increased risk of infection</td>
<td>Most widely studied drug for sarcoidosis</td>
</tr>
<tr>
<td>Prednisolone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-malarial agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloroquine</td>
<td>Chloroquine: 500 mg daily</td>
<td>Nausea</td>
<td>Useful for skin disease</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>Hydroxychloroquine: 200–400 mg per day</td>
<td>Ocular toxicity</td>
<td>and hypercalcaemia</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>10–20 mg per week; dose adjusted for toxicity</td>
<td>Nausea, Neutropenia, Hepatotoxicity, Pulmonary fibrosis (rare)</td>
<td>Useful for chronic sarcoidosis, takes up to 6 months to become effective</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>50–150 mg daily; dose adjusted for toxicity</td>
<td>Nausea, Neutropenia</td>
<td>Not as widely studied as methotrexate, Neutropenia and nausea more common problems than with methotrexate</td>
</tr>
<tr>
<td>Pentoxifylline</td>
<td>400–1200 mg daily; dose-adjusted for toxicity</td>
<td>Nausea</td>
<td>Reports limited to use for acute disease</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>50–200 mg daily; dose-adjusted for toxicity</td>
<td>Somnolence, Teratogenic (major concern), Constipation, Peripheral neuropathy</td>
<td>Most useful for skin disease. Not as effective for pulmonary disease</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Oral 50–150 mg per day Intravenous pulse: 500-1500 mg every 2–4 weeks; dose adjusted for toxicity</td>
<td>Neutropenia, Cystitis, Carcinogenic</td>
<td>Effective but its toxicity limits its use to refractory cases only</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>25–200 mg daily; dose adjusted for toxicity, Blood values used to monitor for toxicity</td>
<td>Increased risk of infection, Renal failure, Hypertension, Carcinogenic</td>
<td>Very variable reports on effectiveness. May be useful for neurosarcoidosis</td>
</tr>
<tr>
<td>Infliximab</td>
<td>5 mg/kg intravenously initially, week two, and then every 4–8 weeks</td>
<td>Increased rate of infection, especially tuberculosis, Allergic reaction to infusion, Cannot give to patient with congestive heart failure, Possibly carcinogenic</td>
<td>Few data about effectiveness Little information about dosage</td>
</tr>
</tbody>
</table>
of hydroxychloroquine compared with other non-steroidal immunosuppressive drugs, hydroxychloroquine was substantially less effective than methotrexate or azathioprine. The cytotoxic agents methotrexate and azathioprine are useful in treating chronic sarcoidosis. However, has not proved a useful guide for therapy. Treatment with ciclosporin significantly reduced T-cell activation as assessed by BAL in patients with sarcoidosis. However, such treatment was not associated with clinical improvement. A randomised trial failed to show any steroid-sparing effects of ciclosporine. Lavage studies have also spurred interest in the macrophage as a potential target for therapy. In particular, TNF α has been investigated in detail. Several groups have shown that alveolar macrophages retrieved by BAL release large amounts of TNF α. Some have noted that increased synthesis and secretion of TNF α by macrophages retrieved by BAL is predictive for persistent disease. In serial BAL studies, TNF α concentrations decreased after successful treatment of sarcoidosis with corticosteroids, methotrexate, or azathioprine. Various other drugs that suppress TNF α release have been used for sarcoidosis. Phosphodiesterase inhibitors such as pentoxifylline block the release of TNF α by alveolar macrophages from healthy people stimulated with lipopolysaccharide, and block spontaneous release of TNF α by alveolar macrophages from patients with sarcoidosis. An open-label trial of pentoxifylline for the treatment of patients with acute, mild, or moderate disease reported efficacy in most patients. However, how many of these patients would have improved without treatment is unclear. Gastrointestinal intolerance was a common side-effect at the doses used. The mechanisms of action of thalidomide are diverse, including an effect on IL 12 release, acting as an antiangiogenesis factor, and blocking TNF α release from alveolar macrophages. In mycobacteria, thalidomide suppresses the granulomatous response without suppressing the host’s ability to kill the organism. The possible effectiveness of thalidomide for sarcoidosis has been lent support by clinical observations of the effectiveness of thalidomide for chronic cutaneous sarcoidosis. Results of a recently completed dose-escalation study of thalidomide for chronic cutaneous sarcoidosis (lupus pernio) showed effectiveness within 2 months with a dose of 100 mg daily. However, thalidomide might not be very useful in the management of some forms of sarcoidosis. Thalidomide therapy in M tuberculosis was associated with enhanced TNF α production. Increased TNF α is a characteristic of active pulmonary sarcoidosis, which might tell us why in one study, thalidomide had no clinically significant effect on pulmonary sarcoidosis. Specific TNF α inhibitors were developed for the treatment of sepsis; these include etanercept, which blocks the TNF receptor and infliximab, which is a murine monoclonal antibody targeted against TNF α. Infliximab has proved useful in treatment of refractory sarcoidosis. It has been noted to increase the risk for tuberculosis either as reactivation or new infection and this risk was higher than that seen with etanercept. Tuberculosis leads to a granulomatous response similar to sarcoidosis. This breakdown in cell mediated immunity with infliximab backs up its use for granulomatous diseases. In a trial of etanercept versus placebo investigators did not show much benefit for patients with chronic sarcoidosis. These findings suggest that anti-TNF therapy helps in some cases of sarcoidosis. However, which drug to use and which patients to treat thus, remains to be established.

Treatment agents for sarcoidosis are summarised in panel 3, which includes the usual doses and most frequently encountered toxicities. The treatment for sarcoidosis has shifted from a list of drugs that affect the lymphocyte to mainly those that affect macrophage function, because in chronic sarcoidosis, TNF α synthesis and secretion could be the most important first pathogenic step. Therefore therapy with drugs directed against TNF α might prove a specific targeted treatment for disease. On the other hand, sarcoidosis remains a multifaceted disease. Combination therapy might treat several aspects of the disease at the same time, as well as reduce toxicity.

Conclusion

New molecular methods have allowed us to ask why patients develop sarcoidosis and why it is such a divergent disease. Continuing familial and sporadic studies in Europe and the USA should provide insight into the various candidate genes. The treatment for chronic sarcoidosis has become a specific goal of the physician. Among the strategies being explored are drugs that affect macrophage function, including the release of TNF α.

Conflict of interest statement

R P Baughman and E E Lower have National Heart Blood and Lung Institute funding in sarcoidosis. They also have been funded for studies in sarcoidosis therapy by Glaxo Smith Kline, Centocor, Immunex, and Celgene. R M du Bois has been funded for studies in sarcoidosis therapy by Glaxo Smith Kline and 3M.

References


