Short Communication: Possible association between sarcoidosis and fungal infection

Hans Schweisfurth

Sarcoidosis is a multisystem inflammatory disease of unidentified aetiology, which manifests as noncaseating granulomas. It is hypothesised that sarcoidosis has an antigenic or inflammatory trigger that initiates the immune reaction in a susceptible host. Research is focusing on the correlation between sarcoidosis and exposure to airborne antigens, such as tree pollen, insecticides, mouldy environments, and inorganic particles. There are indications, that microbial cell wall agents, particularly agents from fungi, even in the absence of clinical infections can cause a late hypersensitivity reaction leading to granulomas. The occurrence of bacterial or fungal infections in sarcoidosis was repeatedly described and DNA or proteins of microbial organisms have been found. Cladosporium species were significantly enriched in specimen of patients with sarcoidosis. It is presumed that different inhaled microbial exposures, including moisture damage, can increase the risk of sarcoidosis, a causal link between mould exposure and sarcoidosis could not yet be proven, but the analysis of tissue samples of patients with sarcoidosis by application of metagenomic sequencing and other techniques identified traces of several fungi.

KEYWORDS aetiology, airborne antigen, bacteria, cladosporium, granuloma, microorganism, metagenomic sequencing, moisture damage

BACKGROUND

Sarcoidosis a multisystem inflammatory disease of hitherto unidentified aetiology, which manifests as noncaseating granulomas, predominantly in the lungs and the intrathoracic lymph nodes. It is believed that sarcoidosis has an antigenic or inflammatory trigger that initiates the immune reaction in a susceptible host. Several susceptibility genes have been identified, but the trigger remains unclear. Granulomatous inflammation is commonly seen in responses to microbial agents, as are other features of sarcoidosis immunopathology, such as oligoclonal CD4 T-cell expansion and T-helper cell (Th) type 1 (Th1) polarization. No microbial cause has been definitively established for sarcoidosis, but candidates include species of Mycobacterium, Propionibacterium acnes as well as fungi. Since sarcoidosis can affect the lungs, eyes, and skin, research is focusing on the correlation between sarcoidosis and exposure to airborne antigens in the environment. Some of the earliest studies of sarcoidosis reported associations with exposure to irritants found in rural settings, such as tree pollen and emissions from wood-burning stoves. More recently, relationships between sarcoidosis and exposure to insecticides, inorganic particles, and mouldy environments have been reported. Progress has been made in identifying the potential causes of sarcoidosis by monitoring patients with newly diagnosed, biopsy specimen-proven sarcoidosis and controls matched by age, sex, race, and geographic area.

Numerous environmental exposures that were moderately linked to sarcoidosis risks, such as agricultural employment, mould or musty odours at work, and pesticide-using industries, were identified. The risk of developing sarcoidosis increased with the extent of tobacco use. Several case series showed an increased prevalence of sarcoidosis in occupations, some of which were accompanied by elevated inhaled exposure to fire-extinguishing emissions, metal and damp work, or rooms with water damage.

IMMUNOLOGIC PATHOGENESIS

The majority of immunologic data available on sarcoidosis are derived from pulmonary studies, since the disease most commonly affects the lungs, although it should be regarded that sarcoidosis does have the capacity to afflict extra-pulmonary organs, sometimes without evidence of concomitant pulmonary involvement. Patients with pulmonary sarcoidosis have increased cellularity of bronchoalveolar lavage (BAL) fluid, with a predominance of CD4+Th cells.

Evidence supports a familial predisposition to sarcoidosis. Alleles of genes involved in antigen presentation, cell signalling, and other immune functions have been
reported to influence susceptibility to the disease, as well as disease course and prognosis. Multiple human leukocyte antigen (HLA) gene alleles have most consistently been shown to be linked to sarcoidosis. Non-HLA genes associated with sarcoidosis also include cytokine, toll-like receptor (TLR), chemokine receptor genes, and others.

These observations suggest that aberrations at multiple levels of the immune response may lead to the disease and that immunogenetic variability may account for the heterogeneity of disease manifestations and course. Also, innate immune mechanisms involving amyloid A might have an influence on the pathobiology of sarcoidosis.

**INFECTION PATHOGENESIS**

There is a hypothesis that microbial cell wall agents, particularly from moulds, even in the absence of clinical infections can cause a late hypersensitivity reaction leading to granulomas. In some cases, the occurrence of bacterial or fungal infections in sarcoidosis was repeatedly described and DNA or proteins of microbial organisms have been found in tissues of patients with sarcoidosis.

*Cladosporium* was significantly enriched in sarcoidosis specimens after adjustment for environmental admixture and multiple comparisons. Fungi of the *Cladosporium* species are extremely common in the environment and can trigger hypersensitivity pneumonitis and asthma and can elicit granulomatous inflammation.

There are several studies demonstrating that the T-cell response in sarcoidosis-affected tissues is strongly polarized toward a Th1 cytokine profile. Expression of interferon (INF) IFN-γ, interleukin (IL) IL-2, IL-12, tumour necrosis factor (TNF) TNF-α, and other cytokines consistent with a Th1 phenotype is upregulated at sites of inflammation in sarcoidosis.

IL-2 is a potent inducer of T-cell proliferation and IFN-γ production and thus plays a key role in the immune response of sarcoidosis. Furthermore, administration of IL-2 or IFN-α has been shown to be associated with new-onset sarcoidosis, or exacerbation of pre-existing disease. Elevated IL-12 levels in BAL fluid, as well as increased production by alveolar macrophages also have been reported in sarcoidosis.

IL-12 promotes Th0 differentiation into Th1 cells and boosts activated natural killer (NK) cells and T-cell proliferation. It also enhances NK and T-cell-mediated cytotoxicity and is a potent stimulator of IFN-γ production. Thus, IL-12 plays a critical role in the immunologic response to intracellular organisms.

Patients with genetic defects in the IL-12/IL-12 receptor system have diminished granuloma formation and are prone to a typical mycobacterial infections.

Increased production of TNF-α, a nonspecific but potent pro-inflammatory cytokine secreted by a variety of immune cells, has been documented in sarcoidosis.

In mouse models of mycobacterial infection, TNF-α and IFN-γ appear to drive granuloma formation, and inhibition of either of these cytokines results in diminished capacity for granuloma formation.

Thus, TNF-α has been proposed as a target for therapy in sarcoidosis, and the use of TNF-α inhibitors has been investigated for the treatment of sarcoidosis but results of clinical trials are conflicting.

Understanding the role of TNF-α in the pathophysiology of sarcoidosis and TNF-α inhibitors as potential therapeutic agents is further complicated by multiple cases of paradoxical development of granulomatous disease following therapy with TNF-α inhibitors that have been reported.

Another key feature of the immunologic response in sarcoidosis is illustrated by the finding that at sites of inflammation in sarcoidosis, T cells exhibit a restricted T-cell receptor (TCR) repertoire, shown to be consistent with oligoclonal expansion, strongly suggesting an antigen-specific response.

The Kveim–Siltzbach test, now seldom used clinically, can offer further immunologic insight. Intradermal injection of the Kveim reagent, which consists of spleen or lymph node extracts from sarcoidosis patients, induces localized granuloma formation in more than 80% of sarcoidosis patients early in the disease process. Furthermore, the site of the Kveim reaction is also infiltrated by CD4+ T cells with restricted TCR heterogeneity.

BAL or peripheral blood monocyte preparations are also capable of inducing a similar reaction.

These findings strongly support that sarcoidosis is caused by an antigen-specific immune response, with mononuclear phagocytes possibly responsible for systemic dissemination of the responsible agent.

In contrast to the described immune response present locally at sites of inflammation, a paradoxical state of anergy in the periphery exists, as evidenced by decreased responses to delayed cutaneous hypersensitivity tests, as well as decreased lymphocyte counts in the peripheral blood of sarcoidosis patients, especially during periods of increased disease activity. The mechanism of this peripheral anergy is unclear although it appears that TRCs may play an important role.

If the aetiology of sarcoidosis is truly related to an infectious agent, a key question is whether this is an active or latent infection or, alternatively, whether sarcoidosis represents an aberrant reaction to remnants of apreviously but only partially cleared organism.

An important hint regarding these questions is the successful use of corticosteroids and other immunosuppressive therapies in the management of sarcoidosis. Despite proposed evidence for the role of an underlying latent infection in sarcoidosis, patients generally do not demonstrate any increased risk of mycobacterial disease or other opportunistic infections while receiving such therapies.

Additionally, for the most part, antimicrobials have not been shown to be helpful in the management of sarcoidosis.
sarcoidosis, apart from tetracyclines and antimalarials, which have a limited role in the treatment of cutaneous sarcoidosis. However, these particular antimicrobials also have anti-inflammatory properties unrelated to their antimicrobial mechanisms of action and generally do not mitigate the need for concomitant corticosteroid therapy for the treatment of the systemic aspects of sarcoidosis.21,22

Although these findings make an active infection seem unlikely in sarcoidosis, there is evidence that sarcoidosis may be transmissible. Bone marrow transplants from patients with sarcoidosis have resulted in granulomatous inflammation in recipients.23,24

Donor macrophages also have been shown to be the origin of granulomatous inflammation in the allograft of a heart transplant recipient who subsequently developed recurrent cardiac sarcoidosis.25

While these examples do not directly indicate active infection, they do suggest that the inciting agent in sarcoidosis may be an antigen contained within mononuclear phagocytes. One plausible explanation of these phenomena is that the immune system effectively overcomes an inciting infection but is unable to completely clear the organism, leaving behind organism remnants which may be intracellularly located to serve as antigens and potentially act as a position for granuloma formation.

In support of this hypothesis, several epidemiological studies describe the association between sarcoidosis and living in a damp and mouldy environment.26–79

Furthermore, in clinical studies in which sarcoidosis was treated with antifungals, greater clinical improvement was reported compared with corticosteroid treatment.80,81

It has been shown that exposure to high levels of fungi and their components present in organic dust represents a risk factor for developing various respiratory symptoms and diseases, such as asthma, hypersensitivity pneumonitis, sick building syndrome, and organic dust toxic syndrome.82–84

Organic dust contains particles of animal, plant and microbial origin, of which the most important in relation to respiratory diseases are fungal beta-glucan and bacterial lipopolysaccharide (LPS).84 Furthermore, bioaerosols with fungi are known to be associated with granulomatous diseases.23,76,85

Previous studies show the in vitro and in vivo effects of fungal cell wall agents (FCWAs) in sarcoidosis. The induced in vitro secretion of cytokines from human peripheral blood mononuclear cells (PBMCs) was higher from subjects with sarcoidosis than controls. A significant relationship was observed between disease severity, measured as chest X-ray scores indicating granuloma infiltration, and the particulate beta-glucan-induced secretion of cytokines.66,67

Patients with sarcoidosis had a significantly higher secretion of inflammatory cytokines TNF-α, IL-6, IL-10, and IL-12 after in vitro co-stimulation of PBMCs with FCWAs and LPS. Co-stimulation with FCWAs and LPS of PBMCs from patients with sarcoidosis caused a weaker reduction of dectin-1, TLR2, and TLR4 receptors expression, which could increase the sensitivity of PBMCs, leading to excessive inflammatory cytokine responses and result in the development or progression of pulmonary sarcoidosis.86

CONCLUSION

There are indications that different inhaled microbial agents frequently detected in moisture damage can increase the risk of sarcoidosis. A causal link between mould exposure and sarcoidosis could not be proven so far, but the analysis of tissue samples of patients with sarcoidosis by application of the metagenomic sequencing and other techniques identified several candidates of fungi including Cladosporium. These findings of microbial enrichment associated with sarcoidosis could be the indication of one cause of this disease. Therefore, it seems necessary in future studies to consider the domestic and professional environment of the patients by asking for inhaled substances including the exposition of moisture damage.

REFERENCES


