Review

Sarcoidosis: Role of non-tuberculosis mycobacteria and Mycobacterium tuberculosis

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ARTICLE INFO

Article history:
Received 16 October 2014
Accepted 18 October 2014
Available online 30 October 2014

Keywords:
Sarcoidosis
Mycobacterium tuberculosis
Non-tuberculosis mycobacterium
Lung

ABSTRACT

Sarcoidosis is a granulomatous inflammatory disease that is induced by unknown antigen(s) in a genetically susceptible host. Although the direct link between Mycobacterium tuberculosis (MTB) infection and sarcoidosis can be excluded on the basis of current knowledge, non-infectious mechanisms may explain the causative role of mycobacterial antigens. Ever since sarcoidosis was first described, its relationship with tuberculosis (TB) has been under-investigated. Whereas some researchers consider sarcoidosis and TB as two examples of the same disease process, others have rejected mycobacteria as playing any causative role in sarcoidosis. Whether they are linked causally or not, clinical evidence makes a differential diagnosis between the two conditions very challenging, particularly in countries with high burden of TB. The present study analyzes the relationship between sarcoidosis and TB and its implications in clinical practice. The coincidence of TB and sarcoidosis and the higher incidence of mycobacterial DNA in biological samples of sarcoid patients have been reported by many authors. In addition, new evidence of a similarity in MTB phenotype in sarcoidosis is provided. Overall, these observations suggest that TB and sarcoidosis may not only share the same etiology, but may even be different aspects of one disease.

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**Introduction**

The incidence of non-tuberculous mycobacteria (NTM) infection has been increasingly reported both in immunocompromised and immunocompetent patients. Pulmonary infections due to NTM and *Mycobacterium tuberculosis* (MTB) are also increasing worldwide [1]. Fast-growing NTM mycobacteria are ubiquitous organisms in the environment and may cause diseases in both healthy and immunocompromised patients. As such, they are a recognized cause of environmentally acquired diseases, including post-traumatic skin, soft tissue, and bone infections, pulmonary disease [2–4], disseminated infection [5] and cervical lymphadenitis [6]. Information about the risk factors for NTM disease is unclear given that the data comes from case reports and retrospective studies. Many factors have been involved in the increased susceptibility of NTM, such as pre-existing lung disease, immune suppression or genetic defects of cell-mediated immunity that may be playing an important role [7]. Sarcoidosis is an idiopathic, multi-organ, inflammatory disease which is characterized by the presence of epithelioid cell, non-caseating granulomas in various organs [8–10]. The lungs, lymph nodes, skin and eyes are the most commonly affected organs [11]. Yet the potential involvement of any organ system contributes to its myriad of clinical manifestations not well understood. The etiology of sarcoidosis remains unknown; its development is complex, with genetic susceptibility and environmental factors that may be playing important roles in the pathogenesis of diseases [12–14]. Furthermore, certain occupations and environmental exposures have been linked to the higher risk of sarcoidosis in some patients [15,16]. Since the lungs are the most commonly affected organ, the search for an etiologic agent has focused on airborne antigens and infectious or non-infectious bacteria [17,18]. The use of molecular tools and techniques demonstrating genomic or protein material of mycobacterial origin in sarcoidosis tissues, along with elevated humeral and cellular immune response to Mycobacterial antigens, may support the hypothesis that mycobacterial antigens may drive some cases of sarcoidosis.

In addition, there is much clinical evidence supporting the similarity between tuberculosis (TB) and sarcoidosis [19–24]. The present study provides a brief overview on the possible role of mycobacterium in the pathogenesis of sarcoidosis with a focus on the role of NTM. Finding a causal link between the concomitant occurrence of TB and sarcoidosis will be a challenge for the future, but will lead to the use of new therapeutic drugs for suppressing lung inflammation in these patients.

**Sarcoidosis**

The immunopathology of sarcoidosis remains elusive despite years of research into this multi-organ disease [25]. However, recent studies have provided new insights into the genetics and immune components involved in the clinical manifestation of the disease. Granulomatous inflammation is believed to be the host immune response to a persistent poorly degradable unknown antigen [25]. Although direct evidence...
is limited, it is thought that \textit{M. tuberculosis} (MTB) induces the sarcoid granuloma reaction [26].

The immune mechanisms that cause this disease start with the antigenic stimulus, followed by T-cell, macrophage and dendritic cell activation via a classic MHC II–mediated pathway (Fig. 1). The etiology of sarcoidosis is intriguing, since a part of its definition (i.e., unknown cause) makes it uniquely different from granulomatous disorders arising from exposure to a known chronically persisting antigen, such as TB, visceral leishmaniasis and chronic beryllium disease [20,27].

**Non-tuberculosis and tuberculosis mycobacterium**

Much remains to be understood in the pathogenesis of NTM infections in humans as most of these organisms appear to lie at the edge of clinical pathogenicity. A combination of a high-infecting dose, long-standing colonization of bacteria, and host immune status decline may trigger an invasive disease whose clinical presentation may be misdiagnosed as a recurrence of the underlying disease [28,29]. An increase in the rate of NTM diseases in Western countries is associated with a decline in the prevalence of TB [30].

Rather than an increase in prevalence, it is most likely due to an increased number of immunocompromised patients following a longstanding disease and to the introduction of more accurate methods for NTM identification. NTM diseases, unlike MTB, are not reportable to public health authorities; therefore, best estimates of their incidence are often based on the progress in laboratory isolation of NTM. This has led to the recognition of several new species associated with human diseases, such as sarcoidosis [31]. It is believed that granulomatous diseases of lungs may be the result of the continued presentation of an unknown poorly degradable antigen [32,33]. With the increased ability to detect NTM presence in sarcoidosis, this raises the possibility that MTB and sarcoidosis may have a similar causal agent, namely NTM, and that these may even be different clinical manifestations of the same disease in the patient.

**Does mycobacterium infection play a role in sarcoidosis?**

Mycobacteria are a class of bacteria which are very similar to other bacteria, but possess some unique characteristics and behaviors which induce many diverse diseases; for example, \textit{M. tuberculosis} causes TB, and \textit{mycobacterium leprae} causes leprosy [34]. Interestingly, both MTB and NTM have been isolated from a majority of sarcoidosis patients [35–41]. Thus, it has been suggested that sarcoidosis may be a clinical manifestation of this group of patients with infection by the mycobacteria who have a strong granulomatous response which diminishes upon elimination of the mycobacteria [42].

To date, both infective (MTB) and non-infective (NTM) mycobacteria have been implicated in sarcoidosis pathogenesis [43]. Despite this, the role of mycobacteria in sarcoidosis remains unclear and needs to be elucidated in the future.

Non-infective agents have previously been implicated as causal agents in sarcoidosis because of their epidemiological association with disease [44], but this concept has not been well understood [45]. Currently, the focus is on infective agents, and the two strongest candidates are Propionibacterium and mycobacterium [46]. Since sarcoidosis was first described, there has always been a belief that the disease is in some way related to MTB [47].

However, the inability to identify mycobacteria by histological staining or culture from pathological tissues continues to be one of the strongest arguments against a potential role for mycobacteria.

Some studies have suggested a promising association between mycobacteria (both MTB and NTM) and sarcoidosis [48]. In particular, slow-growing mycobacteria species with low pathogenic potential, but with the capability of eliciting a type IV immune response, may be important in sarcoidosis. In support of this, Almenoff et al. in 1997 and Farnia et al.
recently were able to isolate and culture mycobacterium from sarcoidosis patients with a similar phenotype to that seen in TB, respectively (Fig. 2A and B), which provides further evidence for a similar causal agent [49–51].

Whether or not mycobacterium in this form induces antigenicity to mimic sarcoidosis pathogenesis is better left to a perspective study which needs to be elucidated in the future.

In order to confirm this hypothesis, it will be necessary to perform large multi-center trials using a central laboratory for mycobacteria sample testing.

**Conflict of interest**

We have no conflict of interest to declare.

**References**


