Review Article

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Concomitant Patterns of Tuberculosis and Sarcoidosis

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Tuberculosis (TB) is caused by infection with Mycobacterium tuberculosis (M. Tuberculosis, MTB) and despite ongoing global efforts for its eradication there were still an estimated 8.7 million new cases and 1.4 million deaths worldwide in 2011 (1). Co-infection with HIV caused 13% new actively infected people resulting in a high mortality rate (48.6 %) among these patients (2). TB is therefore considered as one of the leading causes of death due to infectious diseases worldwide despite the availability of effective and extensive therapeutic approaches (3, 4).

Two TB-related conditions have been reported, namely, active TB and a latent form of TB infection whereby MTB survives in the body without causing overt signs or symptoms of the disease. People with latent TB infection are not infectious and cannot spread the TB bacteria to others. However, if TB bacteria become active in the body and multiply, the person will go from having a latent TB infection to being sick with TB disease and becoming infective. This unmasking of the latent disease may be idiopathic or the result of immunosuppression either from disease directly or from the use of drugs for treatment of other diseases (5).

The first line of defense against MTB is provided by alveolar macrophages, which ingest and sequester the bacilli within granulomatous structures. The control and resolution of the infection also require activated T lymphocytes (6) and Th_1 cytokines (7). Interestingly, genetic defects within the IL-12/IFN−γ pathway have been found in patients with mendelian susceptibility to mycobacterial disease (MSMD) caused by live BCG vaccine or NTM species. This highlights the crucial role of IL-12/IFN−γ axis in the immune regulation of TB (8).

Sarcoidosis is considered an autoimmune disease characterized by multisystem disorder of unclear etiology that involves any organ, but most commonly the lungs and the intrathoracic lymph nodes although the heart, skin and central nervous system are frequently affected (9). Despite the first clinical description of sarcoidosis over 120 years ago, little is known about the pathogenesis of this disease (10). A genetic predisposition to sarcoidosis is evident from epidemiological studies of familial aggregation, differences in disease susceptibility and severity between racial groups and the significantly increased incidence of sarcoidosis in monozygotic twins of affected individuals compared to other siblings (11, 12). More recent results have provided further insights 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 (10, 13). However, it is clear that no one gene drives sarcoidosis and that the genetic risk is composed of numerous genes having a small effect and that it is the combination of these small individual gene effects that influences disease predisposition (13).

Diagnosing sarcoidosis in patients with a high TB burden poses a significant global challenge particularly in developing countries where there is high prevalence of tuberculosis. Both tuberculosis and sarcoidosis are granulomatous diseases; however, TB results in a caseating granuloma as opposed to sarcoidosis, which presents with a non-caseating epithelioid cell granuloma. New cases of sarcoidosis are increasingly being diagnosed in areas endemic for TB due to increased awareness and better availability of diagnostic modalities (14). As described above, sarcoidosis is a multisystem disorder of unknown etiology, characterized by the presence of non-caseating granuloma (15). In the clinical situation, it is often difficult to differentiate sarcoidosis from tuberculosis, especially when caseous necrosis is not seen and acid-fast staining is negative in biopsy tissue of TB patients.

Histopathologic definitions of sarcoidosis are inadequate, because sarcoid granulomas are not pathologically distinct and cannot be distinguished by simple microscopic or histochemical analysis from granulomas due to other causes (16). Non-specific constitutional symptoms such as fever, fatigue, malaise and weight loss are present in approximately one-third of patients whilst a chest X-ray usually shows hilar and mediastinal lymphadenopathy. Other characteristic findings include interstitial lung disease, or occasional calcification of affected lymph nodes (17). Although the lungs are the most common sites of inflammation, sarcoidosis can also involve other organs such as the eyes (intraocular and adnexal), skin, lymph nodes, salivary glands, heart, spleen, liver, and the nervous system (18).

MTB as a possible cause of sarcoidosis has been extensively studied (19-21). Granulomas form in the lungs as a result of the immune response to inhaled MTB and serve as the central site of host-pathogen interaction during MTB infection. The host typically develops several granulomas based on the number of inhaled bacteria (22, 23). Granulomatous inflammation in sarcoidosis is believed to be caused by the presence of an unknown persistent poorly degradable antigen in conjunction with a strong and non-resolving subsequent host response (24, 25). Studies from India have reported patients with TB preceding the development of sarcoidosis or concurrent presence of both diseases (26-28). This supports other evidence describing the coexistence of sarcoidosis and tuberculosis in the same patient (28, 29). The diagnosis of co-existent disease is established most securely when clinico-radiological findings are supported by histological evidence of widespread non-caseating granulomas (30). However, some TB tissues do not have caseous necrosis and even the distinction between caseation and noncaseation is not absolute. MTB DNA detection in sarcoidosis samples by traditional PCR has been used for the pathological study of sarcoidosis; however, it is likely that real-time RT-qPCR analysis of specific mRNAs and microRNAs will be necessary to provide a sensitive, precise, and rapid diagnostic test for sarcoidosis in TB patients (4). As a result, there is still no definitive conclusion as to the relationship of MTB with sarcoidosis (31-36).

In conclusion, diagnosing sarcoidosis in patients with a high TB burden poses a significant global challenge. Current approaches to diagnosis indicate an increased prevalence of sarcoidosis in areas where MTB is endemic. Improved diagnostic tests including combinations of genetics, mRNA and microRNA profiles are likely to provide improved phenotyping of the various types of sarcoidosis. Improved phenotyping of sarcoid patients may result in better personalized medicine for individuals leading to improved quality of life.

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