Editorial

Mycobacterium and sarcoidosis: Old wine in a new bottle

The conundrum of liaison between mycobacterium and sarcoidosis has fascinated clinicians and researchers through ages. The formation of granuloma is an important defense mechanism against many infectious agents like mycobacteria. Moreover, multisystem granulomatous inflammation is the hallmark of sarcoidosis. The initiating event of this widespread granuloma formation is still unknown, but mycobacterium is widely hypothesized to be the main culprit, forming nidus for these granulomas. In the mid-20th century, Scadding isolated tubercle bacilli in some of his sarcoidosis patients.[1] Studies from that era showed presence of high incidence of tuberculosis in sarcoidosis patients, although their conclusions were later debated. Many cases of Boeck's disease (sarcoidosis) were reported following BCG vaccinations.[2] The epidemiologic association between sarcoidosis and tuberculosis was also recorded in literature around that time, notably by G.Z. Brett and Victor Parson.[3,4] Conversely, several other investigators subsequently noted numerous dissimilarities in socio-demographic profiles of the two conditions.[5,6] More recently, in our DNA age, efforts have focused toward understanding immunological and genetic coaptation of these two conditions.

The advent of molecular biology reinvigorated the search for mycobacterial DNA in sarcoidosis patients. Gupta and colleagues compiled the published evidence for the presence of mycobacterial DNA in sarcoidosis patients by various nucleic acid amplification tests (NAAT) in their meta-analysis.[7] However, many of those studies have been criticized for their small sample size and high incidence of false-positive PCR. The authors conclude that despite few reported bias in the individual studies, the balance of evidence from pooled analysis favors association between mycobacteria and sarcoidosis. Using more sensitive technique combining real-time PCR and enzyme-linked immunospot assay (ELIPSOT), Allen *et al*. demonstrated mycobacterial virulence factor superoxide dismutase A (SodA) in sarcoidosis patients.[8] The sequencing showed most of them as MTB SodA; only two were genetically divergent from MTB SodA. Similarly Song and others found presence of another mycobacterial virulence factor MTB catalase-peroxidase antigen (mKatG) as well as MTB 16srRNA in ~40% of their sarcoidosis subjects by *in situ* hybridization.[9] These data suggest presence of mycobacterial proteins preferentially in sarcoidosis patients. However, it is important to emphasize that a mere presence of mycobacterial DNA does not confirm a cause and effect relationship.

Additionally, the demonstrations of mycobacterial antigen and characteristic immune responses provide further evidence of association between the two entities. Seibert, as early as in 1946, noted elevated γ-globulin with remarkably similar spike in tuberculosis and sarcoidosis patients.[10] Historically, delayed hypersensitive immune reaction to Kveim-Siltzbach reagent was hallmark in diagnosis of sarcoidosis. Moller extracted mKatG as one of the antigens from Kveim reagent using a limited proteomic approach and found similar IgG response in more than half of his sarcoidosis patients to recombinant mKatG DNA.[11] Sarcoidosis patients were also found to contain high antimycobacterial heat shock protein antibodies (hsp70).[12] Subsequently, Oswald-Richter and coworkers demonstrated a CD4+ T-cell immune response to various mycobacterial antigens like KatG, Early Secreted Antigenic Target 6 (ESAT 6), SodA, and HSP in bronchoalveolar lavage obtained from pulmonary sarcoidosis patients compared to PPD- and NTM-control.[13] The same author later showed CD+ T-cell response in sarcoidosis when antigens KatG and ESAT6 were presented by antigen presenting cells expressing DRB1*1101, a sarcoidosis susceptible MHC class II allele.[14] These studies have linked interaction between mycobacterial antigens and genetic susceptibility in sarcoidosis subjects. Over the last decade, other studies have also demonstrated many mycobacterial antigens inducing Th1 cell response and cytokine production in sarcoidosis patients. This variety of immunological reactions against mycobacterial antigens probably suggests prior exposure of antigens in vulnerable hosts leading to development of disease process in sarcoidosis.

Although the above evidences are intriguing, the question still remains regarding the precise role of mycobacteria as an etiologic agent of sarcoidosis. This dilemma is further strengthened given the inability to find mycobacterial DNA or antigens in many sarcoidosis tissues. The anomaly is that no clinical or microbiological evidence of mycobacterial infection was found in those patients, and skeptics rightly question why sarcoidosis patients do not have flare-up of mycobacterial infections after immunosuppressant treatment. This is of great relevance, particularly in

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developing nations where tuberculosis is endemic. The role of serum amyloid A in mechanism of sarcoidosis is also noteworthy.[15] Moreover, association of HLA class I and II alleles in sarcoidosis and tuberculosis population is often inconsistent.[16] Besides, other infectious agents such as *Propionibacterium* as well as many noninfectious potential etiologies like organic or inorganic dusts have been proposed, akin to other granulomatous diseases like chronic beryllium disease. Of particular interest is higher incidence of sarcoid-like granulomatous lung disease among the New York rescue fire fighters in the World Trade Center disaster.[17] We can definitely reconcile from these studies that mycobacteria are not the exclusive etiology of sarcoidosis.

Notwithstanding, the research shows a compelling evidence to suspect mycobacterial antigens have an important role in the pathogenesis of sarcoidosis, at least in a subset of patients. The association of non-tubercular mycobacteria and sarcoidosis is less well characterized, but steroid responsive sarcoid-like granuloma has been described following *Mycobacterium avium-intracellular* complex (MAC) infection.[18] Considering mycobacterial antigen being common causative agent, it is likely the same antigen induces an aberrant immune response in a genetically different host that evolves into sarcoidosis. The question that naturally arises is What are the clinical implications of these findings? Is the term "Tuberculous Sarcoidosis", originally coined by Scadding, a definitive clinical entity?[1]

There are anecdotal reports of treating patients with anti-tubercular drugs and steroids in patients with MTB where sarcoidosis was suspected as well.[19] In this regard, multiple reports of sarcoid-like granulomatous lesions after treatment with TNF-α is provocative.[20,21] Some of those patients showed recovery with anti-TB medications in spite of having negative TB skin test, which can be attributed to their immunosuppression. More recently, Drake and colleagues published the data from phase 1b of CLEAR trial showing excellent clinical response in patients with pulmonary and skin sarcoidosis after treatment with broad-spectrum anti-mycobacterial therapy.[22,23] Although initial results are fascinating, those studies raise many questions as well. Besides the methodology, the duration of therapy, side effects of medications and target patient population need to be addressed. The author recognizes ESAT-6 antigen as focus for treatment response, which is the most important virulent factor of MTB but may be seen in some species of NTM as well.[24]

As reported in National institute of health (NIH) website, the trial exploring efficacy of antitubercular therapy in management of sarcoidosis was conducted in India, but the result has not yet been posted.[25] The CLEAR trial is now at phase 2 level. We shall eagerly wait for the results of these studies. The scientific evidence showing association of mycobacterium and sarcoidosis is thought provoking in spite of some ambiguities. The challenge is to bring those evidences from bench to bedside. Besides finding the culprit organism by culture or DNA to fulfill Koch's postulate, the response to treatment might be the closest we can get to providing evidence of the organism as cause of sarcoidosis. Till we succeed in that quest, the definite answer will always remain elusive.

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