Beryllium disease and sarcoidosis: still besties after all these years?

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Despite advances, the pathobiology of chronic beryllium disease and sarcoidosis continue to overlap more than differ http://ow.ly/4n6FcL

Toxic pulmonary disease from beryllium exposure first came to light in the 1930s, soon after the emergence of industrial uses of beryllium alloys. An early manufacturing application for beryllium compounds, as phosphors in fluorescent tubes, was the cause of some of the first known cases of chronic beryllium disease (CBD) (first termed “pulmonary granulomatosis of beryllium workers”). However, the association between beryllium and granulomatous inflammation was controversial at the outset, leading to the moniker “Salem sarcoid” to describe the outbreak of “sarcoidosis” among fluorescent bulb workers at a manufacturing plant in Salem, MA, USA [1]. Despite opposition from the manufacturer and its allies in the state government, H. Hardy convincingly established the relationship between beryllium exposure and granulomatous disease with her landmark analysis of 17 workers from the Salem light bulb factory [2]. Her key insight was to identify the high frequency of latency of disease onset and progression after cessation of exposure. Nearly a century later, despite subtle clinical and radiological differences, the salient features of pulmonary sarcoidosis and CBD continue to be nearly indistinguishable, leading to occasional suggestions that CBD may be simply “sarcoidosis of known cause” [3].

Since the triggering antigen(s) for sarcoidosis remain unknown, and there is no widely accepted animal model of sarcoidosis, some investigators have proposed studying CBD to gain insights about the pathobiology of sarcoidosis [4–6]. The study of CBD confers some substantial advantages. The process can be dissected epidemiologically and pathologically, in a dose–response and temporal fashion, from exposure to sensitisation to overt granulomatous inflammation. A common genetic polymorphism of the human leukocyte antigen (HLA)-DP1 gene (Glu69) markedly elevates risk for beryllium sensitisation and CBD [7, 8], facilitating assessment of gene–environment relationships and identification of at-risk populations [9]. Antigen-specific immunological responses can be characterised in cells obtained by bronchoalveolar lavage [10], and there are viable animal models for some aspects of CBD [6, 11]. Furthermore, since CBD is an occupational disease spanning several sectors of the military and industrial economy, there are funding sources available for its study that are generally not accessible to researchers interested in sarcoidosis.

In practice, the features of sarcoidosis and CBD overlap dramatically. Although sarcoidosis involves extrapulmonary organs in more than half of patients [12], individuals diagnosed with isolated pulmonary sarcoidosis could easily have CBD if exposure to beryllium is not ascertained and tested [13]. Thus, in some [13, 14], but not all [15] studies, clinically significant rates of unsuspected CBD could be identified in sarcoidosis cohorts after careful screening. The anatomic location and morphology of the CBD granuloma is identical to that of sarcoidosis; except for less prominent intrathoracic lymph node enlargement in CBD, the chest imaging features are also alike. Despite all the clinical similarities in diagnosis, disease behaviour differs in a potentially important way: unlike sarcoidosis, CBD generally requires ongoing treatment [16], whereas a high proportion of sarcoidosis cases enjoy spontaneous

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remission. This discrepancy alone raises the possibility of fundamental differences in the pathophysiology of granuloma formation, antigen clearance and/or immune tolerance.

In the past decade, several observations have been made that suggest sarcoidosis is not simply CBD of unknown aetiology. Serum amyloid A (SAA), an acute phase reactant with innate immune properties, was found in sarcoidosis granulomas, but not in granulomas from patients with infections, vasculitis, hypersensitivity pneumonitis, inflammatory bowel disease or CBD [17]. The authors hypothesised that the variable remission rates in sarcoidosis could be the result of SAA persistence or clearance [17]. This line of evidence implies that sarcoidosis itself is a specific disease, even if more than one antigen can trigger it.

A second fundamental advance that differentiates the pathophysiology of sarcoidosis and CBD is the finding that beryllium is not the proximate antigen to which the immune response of beryllium-specific T-cells is directed [18]. Rather, the beryllium cation induces a conformational change in a susceptible HLA-DP2-peptide complex, leading to its recognition as a neoantigen. An endogenous transmembrane protein, plexin A, has been identified as one relevant antigen that becomes an autoantigen as a result of the conformational HLA changes induced by the distant binding of beryllium [19]. It seems likely that this mechanism of neoantigen generation is specific to CBD rather than other T-cell derived immune responses [18].

Interestingly, recent work suggests that autoimmune mechanisms may also be relevant in sarcoidosis. Grunewald et al. [20] demonstrated clonal expansion of a T-cell subset that binds to a specific Type II HLA molecule (DRB01*03) in a cohort of Löfgren’s patients. Modelling of the peptide-binding groove predicted that a self-antigen, probably derived from vimentin, could be the inciting antigen [20]. In prior work, the same group had demonstrated the presence of multiple self-peptides, including vimentin, bound to HLA molecules from sarcoidosis bronchoalveolar lavage cells [21]. However, the pathogenicity of vimentin or other endogenous peptides in the sarcoidosis patient remains unproven, as does the role of endogenous peptides in non-Löfgren’s patients.

Despite the presence of some fundamental differences between sarcoidosis and CBD, there is still sufficient overlap between both syndromes to justify circumspect comparison. In this issue of the *European Respiratory Journal*, Li et al. [22] compare gene expression in peripheral blood mononuclear cells (PBMCs) from individuals with CBD, beryllium sensitisation and healthy controls. They then compared the expression profiles of the genes differentially expressed in CBD to those from sarcoidosis populations [23, 24]. Using pathway analysis and other bioinformatics tools, they were able to identify JAK/STAT signalling as the most highly upregulated pathway in the CBD patients. Their data also provided evidence for the functional importance of JAK signalling in PBMCs from CBD patients by demonstrating beryllium-induced STAT1 phosphorylation as well as a reduction in beryllium-induced lymphocyte proliferation using a JAK2 inhibitor. These data accord with similar findings in sarcoidosis, where the STAT1 pathway has been shown to be the dominant gene expression feature in both granulomatous tissue [23] and peripheral blood [25]. Canonical signalling through the JAK/STAT pathway is necessary for transcription of numerous gene products (e.g. interferon-γ and interleukin 17) known to be relevant to T-helper cell (Th)1 and Th17 immune responses, which are thought to be central to the pathogenesis of sarcoidosis and possibly also CBD [26, 27].

The similar gene profiles exhibited in CBD and sarcoidosis extend prior observations suggesting immunological parallels between the two diseases. Both are known to be caused by HLA-dependent antigen presenting cell interactions with specific T-cell receptors. Thus, HLA genotypes are thought to be the major determinant of disease susceptibility. In addition, several genetic markers of disease severity, such as transforming growth factor-β and CCR5 are identical for both diseases [28–30]. Although the antigens differ, persistent antigen stimulation in both diseases may lead to CD4+ T-cell dysfunction or exhaustion. In CBD, programmed death-1 (PD-1) is most markedly upregulated on beryllium-specific pulmonary CD4+ cells, and its presence is inversely related to beryllium-induced lymphocyte proliferation [31]. Analogously, in chronic pulmonary sarcoidosis, T-cells exhibit an increased PD-1 dependent loss of proliferative response to nonspecific stimuli [32]. These data may help explain the clinical course of individuals with chronic persistent inflammation from retained antigens such as beryllium.

Reassuringly, the present data corroborate the usefulness of peripheral blood transcriptomic signatures for the study of pulmonary granulomatous inflammation [22]. They also extend support for the concept that many aspects of various pulmonary granulomatous diseases share similar immunological profiles [22]. The authors here found 33 gene products that overlapped significantly between CBD PBMCs and sarcoidosis tissue, including CXCL9, STAT1, TAP1, CCL8 and CXCL11 [20]. The most overexpressed gene in the CBD group, CXCL9, has been shown to correlate with the outcome of sarcoidosis [33]. CXCL9, a STAT1-dependent gene that is a T-cell chemoattractant, promotes granuloma formation and is likely to be an important mediator of pulmonary granulomatous inflammation [34–36]. The observation that peripheral blood gene expression profiling can be used to assess pulmonary granulomatous syndromes
raises the possibility that diagnostic or prognostic markers could be developed for clinical use [37–39]. However, given the immunological similarities between sarcoidosis and CBD, the present study suggests that developing expression profiles that reliably discriminate the two entities will be a significant challenge. Analogous to the currently used beryllium lymphocyte proliferation test, it is possible that changes in gene expression after beryllium stimulation may be a more specific distinguishing marker.

Although there have been very significant and disparate advances in the understanding of CBD and sarcoidosis in the past decade, the pathobiology of these two granulomatous diseases continues to overlap more than differ. For now, it seems safe to state that observations in one of the two diseases are a fertile source for hypothesis development in the other.

References


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