

Chronic beryllium disease: a model for pulmonary sarcoidosis?

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Abstract. Chronic beryllium disease (CBD) and pulmonary sarcoidosis are two distinct chronic disorders, sharing the pathological lung hallmark of the non-caseating granuloma and the immunological feature of T cell activation at the site of disease. However, while CBD is a rare occupational disease in which the cause, i.e. the inhalation of beryllium, is well known since a long time, the etiology of sarcoidosis, which is far more common in the general population, is still unknown. Since granuloma formation requires the presence of an immunogenic initiating antigen, it has been hypothesized that sarcoidosis is an antigen-triggered (auto)immune disease. Furthermore, while the study of large populations exposed to beryllium did made possible the identification of distinct genetic susceptibility factors in CBD, only recently the role of some genetic polymorphisms in sarcoidosis has been unraveled. Therefore, it seems likely that the advancement in the understanding of the immuno-pathogenesis of CBD will also help to design focused genetic studies to finally identify the etiology of sarcoidosis. Moreover, it is also possible that some cases of sarcoidosis are instead been caused by the inhalation of beryllium in genetically susceptible individuals.

Keywords: berillium, sarcoidosis, susceptibility

The inhalation of beryllium (Be) in the workplace has been reported since a long time ago as the cause of a chronic lung disorder known as chronic beryllium disease (CBD) or chronic berylliosis (1). The incidence of the acute form of Be disease, relatively often reported in the past and characterized by the clinical and radiological features of an acute chemical pneumonitis, almost completely disappeared as a consequence of the lowering of the levels of Be in the workplace (1). On the contrary and partially unexpectedly, the incidence of CBD remained stable even after the drastic reduction of occupational Be exposure levels, ranging between 2 and 5% of the exposed workers (2). This fact, together with the basic knowledge that the *in vitro* cellular immune response to Be of T cells derived from CBD patients is controlled by the products of the polymorphic class II major histocompatibility complex (MHC) genes

(3), suggested the presence of individual susceptibility factor(s) for the disease. At the pathological level, the hallmark of CBD is the non-caseating immune granuloma in the lung; this finding in transbronchial biopsies of an individual exposed to Be poses the diagnosis of CBD, preferably together with the demonstration of a Be-specific T cell response in a bronchoalveolar lavage (BAL) sample (4). However, if the epidemiological evidence of exposure to Be would not be considered or would be unknown, the establishment of a firm pathological diagnosis would be impossible, being the granuloma of CBD indistinguishable from the granuloma in sarcoidosis (5) and therefore links between these two clinical entities have been hypothesized (6). The non-caseating granuloma holds the key to the diagnosis of sarcoidosis and provides clues to the immunopathogenesis of the disease (Fig. 1).

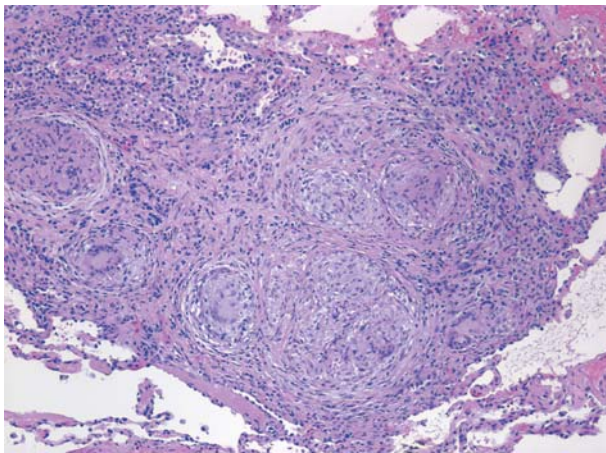


Figure 1. Non-caseating granulomas in a lung biopsy of a patient with a diagnosis of sarcoidosis. The pathological features of these lesions are undistinguishable from those of patients affected by CBD. Slide courtesy of Dr. Giulio Rossi (Pathology Department of the University of Modena and Reggio Emilia)

Sarcoidosis is a granulomatosis that predominantly affects the lungs and is of unknown etiology (7, 8). The presentation and the clinical course of pulmonary sarcoidosis vary widely, from acute self-limited to chronic lung disease, often presenting with phases of recrudescence and phases of clinical remission (8). However, the knowledge of the risk factors for persistent lung impairment and for multiorgan disease in sarcoidosis is limited. These diverse clinical manifestations and progressions help fuel the prevailing hypothesis that sarcoidosis has more than one cause, each of which may possibly promote a different pattern of illness (7). The cause of sarcoidosis probably remained obscure until today also as a consequence of the fact that we are lacking a precise definition and therefore the disorder can have clinical and radiological overlap with other diseases. Moreover, since the etiology of sarcoidosis is unknown, most diagnostic tools are either insensitive or nonspecific: this fact can easily lead to misclassification of patients. In fact, when cases of sarcoidosis have been carefully investigated as “sentinel” health events, physicians sometimes did find a known cause of granulomatous inflammation, such as CBD, hypersensitivity pneumonitis, or mycobacterial and fungal infection; in some cases it has also been possible to detect time- and space-related clusters of sarcoidosis (8).

Evidence of a significant genetic influence in sarcoidosis did become available in recent years, as also reflected by the official international statements (8). Associations between MHC genotypes and sarcoidosis susceptibility/phenotypes are consistent across different ethnic subgroups (9). However, about half of the sarcoidosis patients do not have any evidence for a MHC contribution to pathogenesis (10); this finding underscored the importance of studying other genes, either MHC-associated or located in other chromosomal areas of the human genome (11). Even if genetic factors therefore have a part in the pathogenesis of sarcoidosis, it is highly unlikely that any single gene is fully responsible for the disorder, as in CBD, where a single HLA-DP polymorphism has been shown in different populations to be the main genetic susceptibility factor (12). This is even more true if we consider the effect of the potentially complex interaction between the genetic susceptibility factors and the exposure factors, already studied in CBD (13). CBD risk has been consistently associated with the expression of the supratypic human leukocyte antigen (HLA)-DPB1Glu69 (DPGlu69) marker, a marker that has been found to be expressed in 84-97% of disease cases in three separate studies (12-15), and that has been shown to function as the restriction element for Be presentation to Be-specific T-cell clones from HLA-DPGlu69-positive subjects with CBD (i.e. as the immune response gene of the Be-specific T-cell reaction of CBD) (16). Disease presentation has been associated with major histocompatibility complex (MHC) locus gene markers also in sarcoidosis, where spontaneously resolving hilar adenopathy has been associated with HLA-DR3 and chronic fibrosing lung disease with HLA-DR5 (17).

It has been hypothesized that genetically predisposed hosts are exposed to antigens that trigger an exaggerated cellular immune response and the formation of non-caseating granulomas in sarcoidosis, while in CBD the interaction between the HLA class II polymorphic molecules and the Be molecules in conjunction with the “right” accessory immune genes (such as tumor necrosis factor α) constitute the triggering genotype for the development of the chronic immune reaction that characterizes CBD (15). The genetic differences that promote susceptibility could reside in

loci that influence immune regulation, T-cell function, or antigen presentation or recognition. Recently, it has been reported a strong association between CCR5 haplotype HHC and persistent parenchymal lung involvement in sarcoidosis, as assessed by chest X-ray (18). Even recently, sophisticated genomic analyses prompted by genome-wide screening, in study on sporadic and familiar cases of sarcoidosis has a strong association between a mutated form of the butyrophilin-like 2 (BTNL2) gene and sarcoidosis (19): this study provided invaluable knowledge on the potential role of a particular form of a gene product involved in the mechanisms of T cell activation, therefore suggesting for the first time a precise information on a possible immuno-pathogenetic mechanism of disease. Segregation and linkage analyses in sarcoidosis have not been performed yet and it is likely that they might provide crucial insights. In sarcoidosis, genetic studies may be very relevant not only in defining the risk of disease, but also in determining the pattern of disease, its severity, and prognosis.

The model of CBD, in which subtle single differences in genes coding for HLA class II molecules are strongly associated with increased susceptibility to Be sensitization and the formation of granulomas after exposure to even low levels of respirable Be dust or fumes, will be probably useful in directing the research on genetics of sarcoidosis (6, 20). In the search for genes that may confer susceptibility to sarcoidosis, multiple serologic studies have identified primary associations with class I HLA-A1 and B8, and class II HLA-DR3 in whites (7). For some genetic factors it has already been shown that some polymorphism may be shared as constituents of susceptibility both to Be in CBD and to the unknown antigen(s) in sarcoidosis. As an example, some gene polymorphisms of the pro-inflammatory cytokines are highly likely be associated with the expression of both diseases. One such bi-allelic polymorphism is found in the tumor necrosis factor (TNF)- α gene at position 308 in the promoter region. One of its alleles, the TNFA2 allele, is linked to elevated TNF- α levels. In CBD patients this particular allele is associated with susceptibility to mount an increased T cell response to Be, i.e. to become "sensitized" to the metal after exposure (15). This same TNF- α genotype is not associated with susceptibility

to sarcoidosis, but a shift to the TNFA2 allele has been observed in the subgroup of patients with Lofgren's syndrome (21). Moreover, cases classified as sarcoidosis but more certainly due to "hidden" inhalation of Be have been already described and reported (5, 20, 22, 23). However, it is important to consider that the heterogeneity of the disease-associated HLA polymorphisms in sarcoidosis might, differently from CBD, mirror the heterogeneity of the disease with respect to race, ethnic background, sex, course of disease, etiology and pattern of extra-pulmonary involvement.

In summary, the occupational disease caused by the inhalation of Be provided an invaluable model for the study of sarcoidosis, a more frequent disorder with similar pathological and immuno-genetic features. Moreover, at least some of the patients diagnosed as affected by the latter disease were in fact affected by CBD. The application of the concept of studying disorders of unknown etiology using as a model even rare diseases, but with known cause and immune mechanisms will help to advance medical knowledge. In this context, CBD constitutes a unique model.

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