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An epidemiological perspective on the pathology and etiology of sarcoidosis

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Abstract. To update current knowledge on the pathology and etiology of sarcoidosis, here we review previous epidemiological research and discuss age-related differences and historical changes in the clinical characteristics of sarcoidosis we identified over the last four decades in Japan. Extrathoracic lymph node involvement was more common in young patients, while extrathoracic involvement of non-lymphatic organs and hypercalcemia were more common in older patients. Most patients in their 20s presented with bilateral hilar lymphadenopathy, but this was consistently less common among older patients. Over time, the distribution of age at diagnosis has shifted toward the older age group in the United States, Denmark, and Japan. In Japan, the incidence rate has been decreasing among young people, but there has consistently been a second peak among postmenopausal women. Age-related differences in the clinical presentation of sarcoidosis may reflect the pathways of causative antigens and the strengthening of immunoregulatory mechanisms with age. Internal and external environmental factors, such as exposure to diverse microorganisms, ovarian insufficiency, and active vitamin D deficiency, that may contribute to the onset of sarcoidosis must be identified in order to develop strategies for prevention and treatment. *(Sarcoidosis Vasc Diffuse Lung Dis 205; 33: 112-116)*

Key words: age, epidemiology, estrogen, sarcoidosis, vitamin D

Abbreviations list:
ACCESS=A Case Control Etiologic Study of Sarcoidosis;
BHL=bilateral hilar lymphadenopathy;
BTNL2=butyrophilin-like 2;
HLA=human leukocyte antigen;
IL=interleukin;
IMID= immune-mediated inflammatory disease;
MS=multiple sclerosis;
Th1=T helper 1 cell;
Treg=regulatory T cell

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1. Introduction

Sarcoidosis is considered to be an amplified and persistent granulomatous reaction to inhaled antigens that develops when an individual with genetic predisposition encounters some kind of environmental change. However, the exact mechanisms involved are unclear. One focus of study has been the 6p21.3 locus on the short arm of chromosome 6, which includes the human leukocyte antigen (HLA) gene class II domain and the butyrophilin-like 2 (BTNL2) gene, and recently several novel susceptibility loci related to interleukin (IL)-23/IL-12 signaling pathways were identified (1). Polymorphisms within these regions are potential risk factors for sarcoidosis, influencing the ability of T-helper type 1 (Th1) and Th17 cells to process antigens and regulatory T cells (Tregs) for immune response modulation

(2-4). As yet though, there is insufficient evidence of the involvement of either external or internal environmental factors acting within an individual. To update current knowledge on the pathology and etiology of sarcoidosis, here we review past epidemiological research and discuss age-related differences and historical changes in the clinical characteristics of sarcoidosis we identified over the last four decades in Japan (5).

2. Age-related differences in organ involvement and chest radiographic staging

The ACCESS study (A Case Control Etiologic Study of Sarcoidosis) showed that almost all sarcoidosis patients had pulmonary involvement, regardless of race, sex, or age (6). Patients under 40 years of age were more likely to have involvement of the extrathoracic lymph nodes, whereas those more than 40 years of age were more likely to have abnormal calcium metabolism (6). Our recently published single-institution observation study conducted in Japan showed similar trends: involvement of the extrathoracic lymph nodes, salivary glands, and liver was more common among patients aged < 45 years; hypercalcemia and involvement of various non-lymphatic extrathoracic organs including the eye, heart, muscle, and kidney were more common among older patients (≥ 45 years) (5). Moreover, most patients in their 20s presented with bilateral hilar lymphadenopathy (BHL), but this was consistently less common among older patients (7).

These age-related differences in organ involvement are consistent with the presumed pathology of sarcoidosis: the causative antigen enters via the lungs during the early stage of the disease and affects the regional intrathoracic lymph nodes, then circulates via the lymphatic and vascular systems to affect the extrathoracic lymph nodes, liver, and spleen (8). Furthermore, the age-related differences in chest radiographic staging may reflect both the proliferation of Th1 and Th17 cells after antigen presentation by dendritic cells in the thoracic lymph nodes (2, 9) and the strengthening of immune regulation with age. It is known that the mechanisms of proliferation of effector T cells in the thoracic lymph nodes are generally affected by this strengthening of the immunoregulatory mechanisms with age and is thus a major determinant of the progressive decline in immune responses that come with aging.

A statement on sarcoidosis that was released in 1999 states that "an acute onset with BHL usually heralds a self-limiting course, whereas an insidious onset, especially with multiple extrapulmonary lesions, may be followed by relentless, progressive fibrosis of the lungs and other organs" (10). This suggests that immunoregulatory balance might influence not only organ involvement at diagnosis and the nature of onset, but also the clinical course of sarcoidosis.

3. Historical changes in the distribution of age at diagnosis

a) Increasing patient age at diagnosis

Sarcoidosis is generally thought to occur more frequently in adults younger than 40 years of age, with incidence peaking between 20 and 29 years (10). However, in recent decades, evidence has emerged of an upward shift in age at diagnosis over time in the United States and Denmark (6, 11). A similar shift has been observed over the last four decades in the relatively genetically homogeneous Japanese population, reflecting - at least in part - a decreased incidence in the young (5, 12). This suggests modification of the age-specific distribution of sarcoidosis as a result of environmental factors.

This recent decrease in incidence among young adults might to some extent reflect fewer opportunities for exposure to various rural environmental triggers in early life. Previous epidemiological studies have shown that living in rural areas and working in agriculture are associated with the incidence of sarcoidosis (13-15), and there is increasing epidemiological evidence that exposure to microbial-rich environments increases the risk for sarcoidosis development (14): individual exposure to various microorganisms might not only increase opportunities for the causative antigen to invade the lungs, but also modify susceptibility to the disease. The diversity and intensity of microbial stimuli to which we are exposed, especially during early childhood, are known to affect the innate immune system and subsequently cause immune deviation toward an enhanced Th1 response. More detailed role of microorganisms in the etiology of sarcoidosis needs to be determined.

b) The persistent second peak in women

In Japan as well as Europe, the distribution of age at diagnosis is biphasic in the case of women, with a second peak appearing after 45 years of age. Although we noted in the previous section that there has been a recent decline in the first peak, the second peak in women aged ≥ 45 years has been consistently maintained in Japan over the last four decades (5). Furthermore, we have encountered 3 consecutive patients who developed sarcoidosis during etanercept treatment for rheumatoid arthritis in women with a history of bilateral oophorectomy [Sarcoidosis Vasc Dis 2006 (in press)]. These findings imply that the onset of sarcoidosis is potentially accelerated by insidious ovarian dysfunction associated with menopause. Early clinical observations among women with a previous diagnosis of sarcoidosis have revealed postpartum relapse as well as remission during pregnancy, suggesting that certain female reproductive and hormonal factors may reduce disease activity. Furthermore, in 2012, epidemiological research carried out in the US Black Women's Health Study suggested that endogenous female hormones could possibly protect against the onset of sarcoidosis (16).

Based on experimental findings of enhanced Th1 granulomatous reactions after bilateral oophorectomy (17, 18), it appears that a sudden decline in circulating ovarian hormones promotes the development of granulomatous diseases by forming local Th1 cytokine environments, followed by migration of T cells. Increased expression of the transcription factor T-bet due to loss of the immunomodulatory effects of ovarian hormones has been noted to induce local Th1 cytokine environments (18), which could increase susceptibility to granulomatous reactions in sarcoidosis (19). The possibility that estrogen insufficiency, which affects antimicrobial activity in macrophages, may lead to amplified granulomatous reactions in the lungs cannot be ruled out (20). Moreover, a prolonged decrease in the levels of ovarian hormones is known to systemically promote Th1 cell differentiation and markedly reduce the Treg cell population (21); eventually, this may partly contribute to the amplification of granulomatous reactions.

Given the considerable number of women diagnosed with sarcoidosis in the pre-menopausal stage, this proposed mechanism is still speculative. Further studies are needed to clarify whether there is a difference in disease between pre-menopausal and post-menopausal women.

4. Latitude-based differences in incidence

The incidence of sarcoidosis has been found to be greater at higher latitudes during winter, where there is less exposure to ultraviolet rays. Among the residents of these regions, Black individuals were found to have a particularly high incidence, as the ability to convert 7-dehydrocholesterol to previtamin D_3 is suppressed due to skin pigmentation (22, 23). These epidemiological observations imply that a deficiency in $1,25(OH)_2D_3$, the active form of vitamin D, may contribute to the onset of sarcoidosis.

As intracellular microorganisms are the likely carriers of triggering antigen, adequate $1,25(OH)_2D_3$ levels may suppress the development of sarcoidosis by increasing the antimicrobial activity of macrophages (22, 23). Deficiency in $1,25(OH)_2D_3$ has been shown to be associated with decreased production of the antimicrobial peptide cathelicidin, and consequently contributes to the onset of tuberculosis (23). The finding that other infectious granulomatous diseases tend to be more common in Black individuals serves as indirect evidence that $1,25(OH)_2D_3$ deficiency contributes to the onset of these diseases (23). Analysis of bronchoalveolar lavage fluid from patients with sarcoidosis has shown that cathelicidin production is low compared with that in healthy controls (24). Furthermore, adequate $1,25(OH)_2D_3$ levels may prevent the development of sarcoidosis by suppressing Th1 immune responses while boosting immune regulation (22, 23, 25, 26).

It seems contradictory that higher levels of $1,25(OH)_2D_3$ were associated with increased disease activity and protracted treatment (27). Hypercalcemia in patients with sarcoidosis may reflect local vitamin D activation within the granulomas, and measurement of serum $1,25(OH)_2D_3$ appears to correlate best with vitamin D status (28). However, one case report proposed that hypercalcemia reflects local vitamin activation, with the serum concentration of activated vitamin D being conversely low (29). Further research is needed on these issues, including whether or not vitamin D deficiency is a risk factor for sarcoidosis.

5. Suggestions for prevention and treatment strategies

Due to similar clinical and epidemiological characteristics between sarcoidosis and immune-mediated inflammatory diseases (IMIDs) such as Crohn's disease and multiple sclerosis (MS), possible common etiological pathways have been highlighted (30). In fact, a recent study has demonstrated that a considerable number of susceptibility factors are shared between sarcoidosis and these IMIDs, including the IL-23/IL-12 signaling pathway (1). This suggests that the immunological etiology of disequilibrium between the Th1 and Th17 response and regulatory mechanisms is common to both disorders. However, the monoclonal antibody against IL-12/23 p40, which blocks the proliferation pathway shared by Th1 cells and Th17 cells, has not shown sufficient therapeutic effect against sarcoidosis (2,30). Amplification of Th1 cells plays a central role in both disease development and remission by removing the antigenic stimulus, and this might partly explain the difficulty in managing sarcoidosis. To restore the function of global CD4 subsets and to preserve the homeostasis between inherent Th1 responses and immunoregulatory mechanisms, it has been proposed that researchers search for therapeutic targets in the early stages of T cell differentiation (31). Furthermore, vasoactive intestinal peptide, which restores Treg function, shows promise for clinical application (32).

On a global scale, the epidemiology of MS, which results from a breakdown of immune tolerance to the individual's own central nervous system antigens, closely resembles that of sarcoidosis, including a second incidence peak in postmenopausal women and a greater incidence in individuals living at higher latitudes. It is emerging that factors such as ovarian insufficiency and active vitamin D deficiency due to inadequate exposure to ultraviolet rays may contribute to disease onset, in part by reducing the immunoregulatory abilities of Tregs. Therefore, administration of estrogen or vitamin D (33) is expected to prevent and treat MS by restoring Treg quantity and quality. As one aspect of the pathology of sarcoidosis is the breakdown of immune tolerance to foreign antigens that enter via the lungs, such management strategies may have a similar effect on sarcoidosis.

6. Conclusion

In this epidemiological review, we have presented current knowledge on the etiology and pathology of sarcoidosis from various perspectives, including the pathway of causative antigens, reduced ability of macrophages and Th1 cells to process antigens, and disequilibrium between the Th1 and Th17 responses and regulatory mechanisms. Environmental risk factors that contribute to onset must be identified among such candidates as exposure to diverse microorganisms, ovarian insufficiency, and active vitamin D deficiency in order to develop strategies for prevention and treatment of sarcoidosis. Owing to major advances in diagnostic imaging technologies and diagnostic criteria (34), it is now possible to diagnose atypical cases, compile more detailed patient data, and perform more extensive epidemiological research.

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