Cardiac involvement is an important prognostic factor in sarcoidosis. Corticosteroids are the mainstay of treatment in cardiac sarcoidosis (CS) to control the inflammatory process regardless of clinical presentation. Although the effect of steroid therapy on long-term outcome has not been established in large, well-controlled trials, a relatively large number of published clinical experiences supports the clinical efficacy of this treatment for CS. Early initiation is essential to prevent progression of cardiac dysfunction and may improve clinical outcome. However, when should we start? In other

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Figure. Possible mechanism of granuloma formation and clinical findings in cardiac sarcoidosis. APC, antigen-presenting cell; FDG, fluorodeoxyglucose; Ga, gallium; IL, interleukin; MCP, monocyte chemoattractant protein; MIP, monocyte inflammatory protein; MRI, magnetic resonance imaging.
words, whether treating such asymptomatic patients is of benefit is yet to be determined. In addition, the beneficial effect of corticosteroids for CS patients with endstage heart failure remains controversial. The most difficult problem is that we do not have reliable markers or imaging modalities to evaluate inflammatory activity and to guide corticosteroid treatment in patients with CS. The study by Orii et al published in this issue of the Journal might provide precious information about disease activity in CS patients treated with corticosteroids.

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**Evaluation of Inflammatory Activity by Imaging Modalities**

Active inflammation can be detected by gallium-67 accumulation, although the sensitivity for detection of cardiac involvement is lower than for other radionuclide tests. There is an important role of F-18 fluoroexyglucose (18F-FDG) positron emission tomography (PET) for assessing disease activity and guiding medical therapy in patients with CS. Although 18F-FDG PET is significantly more sensitive than gallium-67 scintigraphy, it should be noted that the specificity of PET with 18F-FDG for detection of CS remains variable because low specificity may be related to physiological myocardial uptake of 18F-FDG in the normal heart. Furthermore, several authors have proposed various abnormal findings, such as uptake patterns including focal or focal-on-diffuse pattern, mismatches with perfusion, SUV or coefficient of variation (COV) of the SUV suggestive of CS. Because standardization of preparation protocol and interpretation have not yet emerged, the Japanese Society of Nuclear Cardiology has published "recommendations for standardized 18F-FDG PET imaging for CS". Orii et al adopted the COV of the SUV as a marker of inflammatory activity in CS. Tahara et al demonstrated that heterogeneous uptake in the heart shown by the COV of the SUV on 18F-FDG PET is highly suggestive of CS (sensitivity: 100%, specificity: 97%) as compared with dilated cardiomyopathy or healthy control. However, this index has not yet been standardized as per the PET recommendation, because their study included only 12 CS patients. To evaluate inflammatory activity by 18F-FDG PET, we need to validate whether the COV of the SUV is the most appropriate interpretation or not.

**Immunologic Mechanism of Granuloma Formation (Figure)**

The development and accumulation of epithelioid cell granulomas are essential in the pathology of sarcoidosis. The immunologic mechanism of granuloma formation is not fully understood. The presence of CD4+ T cells that interact with antigen-presenting cells is important to initiate the formation of granulomas. Type 1 helper T (Th1) cells are differentiated from these activated CD4+ T cells and secrete predominantly interleukin-2 and interferon-γ. Th1 cells enhance tumor necrosis factor (TNF)-α production from macrophages and amplify the cellular immune response in various organs and tissues of sarcoidosis patients. Macrophages, in the face of various cytokine stimulation, differentiate into epithelioid cells, gain secretary function, and form multinucleated giant cells. The pathogenesis of fibrosis after granulomatous inflammation in sarcoidosis remains unknown, but matrix metalloproteinases and a shift from cytokines produced by Th1 cells to type 2 helper T cells may also be related to the development of fibrosis. Although recruitment of monocytes to target organs and tissues is critical in the granuloma formation of sarcoidosis, the peripheral monocyte subpopulation in CS is not been well understood.

**Peripheral Monocyte Subpopulation and Sarcoidosis**

Human monocytes can be divided into 3 subpopulations: classical (CD14++CD16−), intermediate (CD14++CD16+), and non-classical (CD14+CD16++). Those monocyte subpopulations have been investigated in a variety of autoimmune diseases, including extra-CS, and atherosclerosis. It appears that Orii et al’s paper is the first reported study assessing the relation between monocyte subpopulations and disease activity in patients with CS. They demonstrated that CD14++16+ monocytes were upregulated in CS patients, followed by a significant decrease after corticosteroid therapy. Cytometric analysis of the peripheral monocyte subpopulation might provide useful information in patients with CS treated with corticosteroids. They suggest that the proportion of CD14++16+ monocytes may reflect the activity of cardiac inflammation, and may be a surrogate marker of the therapeutic effect of corticosteroids in patients with CS. However, they did not confirm the immuno-histochemical findings on CD14++16+ monocytes using endomyocardial biopsy specimens. It remains unclear whether the elevation in the proportion of circulating CD14++16+ monocytes reflects the extent of monocyte infiltration into the myocardium. Cytokines and chemokines interacting with their receptors are known to have a crucial role in recruitment of inflammatory cells in myocardial lesions. TNF is thought to play a key role in the development of granulomatous inflammation, so it is a major target for immunosuppressive therapy in sarcoidosis. A recent report has demonstrated that intermediate monocytes (CD14++CD16+) show the highest expression level of TNF-receptor 1 among monocyte subpopulations in patients with sarcoidosis, which supports the results of Orii et al regarding the monocyte subpopulation and disease activity.

**Clinical Implications in Patients With Systemic Sarcoidosis and Isolated CS**

Because sarcoidosis is a systemic disease involving multiple organs and tissues, immunologic variables obtained from peripheral blood are influenced by inflammatory activity not only in the heart, but also extracardiac organs and tissues. On the other hand, isolated CS characterized by cardiac signs and symptoms as the first manifestation and no clinical evidence of extracardiac involvement such as lung, lymph nodes, skin and/or eye, and only 2 of the 10 cases were isolated CS. It cannot be decided whether the proportion of CD14++CD16+ monocytes in peripheral blood really reflects inflammatory activity only in the heart. To confirm their results, we need to study each subpopulation in CS patients with extracardiac lesions and isolated CS. Although there are several limitations to validate, as mentioned above, the results from Orii and coworkers may provide new insights into evaluating inflammatory activity and guiding corticosteroid treatment in patients with CS.

**Disclosures**

The author states that he has no Conflict of Interest (COI).

**References**


