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REVIEW

Historical transition of management of sarcoidosis

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Abstract

Sarcoidosis is a systemic granulomatous disease of undetermined etiology, and it primarily affects the lungs and lymphatic system but may involve other organs. Recently, there have been several new insights in Japanese patients. The frequency of cardiac, ocular, and cutaneous sarcoidosis has increased in Japan, whereas, the proportion of patients with bilateral hilar lymphadenopathy decreased from 1960 to 2004. *Propionibacterium acnes* (*P. acnes*) has been studied extensively as one of the causative microorganism for granuloma formation, particularly in Japan. *P. acnes*-specific monoclonal antibodies are useful for diagnosing sarcoidosis. The potential association between smoking and sarcoidosis has been evaluated in a Japanese study, which found a higher prevalence of sarcoidosis among young smokers than that in previous reports. Recently, ^{18}F-fluorodeoxyglucose positron-emission tomography, which permits visualization of activated inflammation, and endobronchial ultrasonography-guided transbronchial needle aspiration have been increasingly used to diagnose sarcoidosis. Cardiac sarcoidosis is found to be the main cause of death in Japan. The 2006 revised Japanese guidelines for diagnosing cardiac sarcoidosis are useful, particularly for subclinical cardiac sarcoidosis patients. Further studies and international communication and evaluation are needed to determine the causes of sarcoidosis, identify the risk factors for progressive disease, and develop new and effective treatments.

Key words: Japan; *Propionibacterium acnes*; Smoking; Cardiac sarcoidosis; Positron-emission tomography; Endobronchial ultrasonography-guided transbronchial needle aspiration

Core tip: Sarcoidosis, a systemic granulomatous disease of undetermined etiology, is characterized by a variable clinical presentation and course. *Propionibacterium acnes* (*P. acnes*)-specific monoclonal antibodies can detect *P. acnes*, a causative microorganism, and are useful for diagnosing sarcoidosis. The importance of ^{18}F-fluorodeoxyglucose positron-emission tomography and endobronchial ultrasonography-guided transbronchial needle aspiration to diagnose sarcoidosis is progressively increasing. Cardiac sarcoidosis is the main cause of death in Japan. The 2006 Japanese guidelines for diagnosing cardiac sarcoidosis are useful, particularly for subclinical cardiac sarcoidosis patients. Further

studies and international communication and evaluation are needed to improve our management of sarcoidosis.

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INTRODUCTION

Sarcoidosis is a multisystem granulomatous disease that primarily affects the respiratory and lymphatic systems. The disease occurs worldwide, affecting both sexes and all ethnicities[1]. Although sarcoidosis may occur at any age, it is usually seen in adults under the age of 50 years. The pathogenesis of sarcoidosis involves antigen exposure in a genetically susceptible host, resulting in a typical granulomatous inflammatory response, with an increased CD4/CD8 T cell ratio (a Th1 cell-mediated immune response). A diagnosis of the disorder usually requires the demonstration of typical lesions, characterized by non-caseating epithelioid cell granulomas in more than one organ system, and exclusion of other disorders known to cause granulomatous disease. The clinical course of sarcoidosis ranges from an incidental finding and spontaneous remission to a devastating life-threatening disease. Although fibrosis can gradually develop in the insidious form of sarcoidosis, especially with extra-pulmonary, multi-organ involvement, no clinical parameters allow an accurate prediction of the clinical course. The clinical phenotype varies in different areas and among different ethnic groups. In Japan, sarcoidosis has a low incidence and prevalence, and is less severe than in western countries[2]. Sarcoidosis in Japan is reported to have a much higher likelihood of ocular and cardiac involvement than in the West[3]. This review summarizes recent advances in the management of sarcoidosis.

EPIDEMIOLOGY

The epidemiological characteristics of sarcoidosis differ between geographical regions, probably owing to differences in environmental exposures and predisposing genetic factors. Details on the reported prevalence of specific organ involvement among different ethnicities are described in the "Diagnostic Criteria and Organ Involvement" section.

In Japan, the Ministry of Health, Labour, and Welfare has designated sarcoidosis as an intractable disease, and clinical characteristics of newly diagnosed disease are registered nationwide. By using this system, we evaluated clinical phenotypes of pathology-confirmed sarcoidosis diagnosed in 2004, and compared findings with those of previous surveys in Japan[4]. The female/male incidence ratio increased from 0.49 in 1960-1964 to 0.65 in 2004. The frequency of eye and skin involvement and cardiac abnormalities increased in 2004. In contrast, the proportion of patients with bilateral hilar lymphadenopathy decreased from 90.7% in 1960-1964 to 75.8% in 2004. These results suggest that the clinical characteristics of sarcoidosis have been changing, probably as a result of the aging of the population, and changes in environmental and social factors, including advances in diagnostic procedures (discussed in the "Diagnostic Approaches" section). Of note, our recent analysis, based on this database, also showed that the age at onset among newly diagnosed subjects increased from 2000 to 2009 (unpublished data). Accordingly, repeated large-scale surveys are warranted to keep up with the significant changes in the clinical manifestations of this disease under the recent drastic aging of the Japanese population.

PATHOGENESIS

Potential infectious pathogens

Although the exact causes of sarcoidosis remain unclear, the current working hypothesis suggests that the condition is caused by alterations in immune response after exposure to infectious agents in genetically susceptible individuals. Mycobacterial organisms are one of the most commonly implicated potential etiological agents, based on studies using polymerase chain reaction (PCR) methods that have reported the detection of microbial DNA from these organisms in tissues from patients[5-7].

One clinical observation that serves as a bridge to the cause of sarcoidosis is the Kveim reaction, representing the development of local epithelioid granulomas several weeks after the intradermal injection of homogenized sarcoidosis tissue[8,9]. Using a proteomics approach, based on the physicochemical properties of the Kveim reagent, Chen *et al*[10,11] detected a limited number of poorly soluble antigenic proteins in sarcoidosis tissues and identified *Mycobacterium tuberculosis* catalase-peroxidase protein (*mKatG*) as a potential antigen causing the disease. In addition, DNA for the *mKatG* gene has been identified in archived sarcoidosis biopsy specimens and immunoglobulin (IgG) responses to recombinant *mKatG* were exhibited in nearly 50% of patients with sarcoidosis[12], providing further evidence of a mycobacterial etiology for at least a subset of sarcoidosis cases.

Together with mycobacteria, the commensal bacterium *Propionibacterium acnes* (*P. acnes*) has been studied extensively as one of the causative microorganism for this disease, particularly in Japan. Predominantly found in the cutaneous flora, latent infection by *P. acnes* has been implicated as one of the potential cause of sarcoidosis, since it is the only microorganism that has been isolated in bacterial cultures from sarcoid lesions[13,14].

To elucidate the causative links between sarcoidosis

and *P. acnes*, Negi *et al*[15] screened for this bacterium in sarcoid and non-sarcoid tissues using immunohistochemical methods with novel *P. acnes*-specific monoclonal antibodies that react with cell-membrane-bound lipoteichoic acid (PAB antibody). They showed a high frequency and specificity of *P. acnes* detected by PAB antibody[15], indicating that this indigenous bacterium might represent one of the cause of granuloma formation in a subset of sarcoid patients. Moreover, given the high specificity of PAB antibody in subjects with sarcoidosis, Yi *et al*[16], Minami *et al*[17] and Nishiwaki *et al*[18] emphasized that this antibody may be useful for diagnosing sarcoidosis caused by *P. acnes*. Notably, sarcoid granulomas can be experimentally induced in mice by the administration of a recombinant trigger-factor protein from *P. acnes*[16-18]. An association between *P. acnes* and sarcoidosis was indicated by meta-analysis[19], but the control surveillance on the prevalence of the agent in non-sarcoidosis subject has not been enough, and the direct pathogenic role in the development of sarcoidosis has yet to be determined in humans. Further studies are needed to elucidate the working hypothesis for the pathogenesis of this disease, as "an allergic endogenous infection caused by certain pathogens." Possible treatment strategies for this disease on the basis of this hypothesis are discussed in the "Treatment" section in this article.

Environmental factors

A number of environmental risk factors for sarcoidosis have been proposed based on previous surveys conducted in different districts and among different ethnic groups. The Design of A Case Control Etiologic Study of Sarcoidosis (ACCESS) study, which collected data on 704 patients with sarcoidosis and age- and sex-matched control subjects, identified modest associations between several environmental exposures and sarcoidosis risk, including agricultural employment, mold or mildew, musty odors at work, and pesticide-using industries[3,20]. However, these findings were inconclusive and have not been well replicated elsewhere around the world.

The potential association between smoking and sarcoidosis has been evaluated in several studies, and surveys conducted in Western countries have demonstrated a significantly lower prevalence of smokers among subjects with sarcoidosis than among control subjects[21,22]. To evaluate whether a negative impact of smoking on the development of sarcoidosis would also be seen in the Japanese population, which has a high prevalence of smokers, we retrospectively evaluated smoking status in 388 patients newly diagnosed with sarcoidosis in Sapporo City, Japan between 2000 and 2008[23]. That survey showed that the prevalence of smokers with sarcoidosis was not as low as in the general population, or rather, was surprisingly higher in young subjects (20-39 years old). Although the exact reasons for this marked difference in associations between Western countries and Japan are unclear, differences in genetic background may be associated with sensitivity to smoking. This result emphasizes the significance of epidemiological surveys for different ethnic groups and regions to clarify environmental factors associated with this disease.

Genetics

Racial differences and familial clusters suggest a genetic predisposition for the development of sarcoidosis. A number of susceptibility loci have been identified from a classical candidate gene approach, with human leucocyte antigen (HLA) class Ⅱ alleles representing the main contributors to disease susceptibility across different ethnic populations[24,25]. In addition, recent advances in genome-wide association studies have suggested novel genes and loci conferring susceptibility to sarcoidosis[26-30]. *BTNL2* gene polymorphisms were previously linked to sarcoidosis susceptibility[26]. Recently, a single nucleotide polymorphism (SNP) within *BTNL2* was associated with disease susceptibility to sarcoidosis in Japanese[31], and results for genes such as *ANXA11* have been replicated in different ethnicities[32-36]. In sarcoidosis patients, other SNPs within *ANXA11* were associated with essential functions in several biological pathways, including apoptosis and proliferation[27]; C10ORF67 with mucosal inflammation and manifestation of sarcoidosis[37]; RAB23 with the sonic hedgehog pathway in sarcoidosis pathophysiology[35]; NOTCH4 with regulating T cell immune responses and endothelial differentiation, apoptosis and proliferation[35]; and *CCDC88B* with the regulatory function of several genes[30].

However, most variants identified to date appear to confer relatively small increments in risk, and explain only a small proportion of familial clustering. Potential sources of this so-called missing heritability include the heterogeneity of this disease resulting from complex interactions between multiple genetic and environmental factors. Phenotypic classification of the disease and consideration of environmental factors could thus reduce disease heterogeneity and contribute to the identification of novel associated genes. In this regard, genetic associations have been demonstrated along phenotypic lines, rather than with the entire disease population, such as with Löfgren's syndrome[38-40], chronicity of the disease[41-43], disease with organ-specificity[44-46] and prognosis of the disease[47-53] (discussed in the "Prognosis" section). A significant interaction between certain HLA DRB1 alleles and subjects with sarcoidosis and exposure to insecticides or mold has also been demonstrated[54]. Further studies that consider genetic-phenotypic and genetic-environmental interactions should help unravel the heterogeneous pathogenesis of this disease and its unclear cause.

DIAGNOSTIC APPROACHES

There is no single diagnostic test for sarcoidosis. The

diagnostic approach relies on clinical manifestations, several serum or urine markers, radiological findings, histological evaluation, and exclusion of other diseases capable of producing a similar histological or clinical picture[46].

Biomarkers

Serum biomarkers of inflammatory activity are needed to manage patients with sarcoidosis. Conventional serum markers for sarcoidosis activity such as angiotensin-converting enzyme (ACE) and soluble interleukin-2 receptor (sIL-2R) may be increased even though the patient does not have any symptoms or functional impairment. Sarcoidal granulomas produce ACE, and ACE levels are elevated in 60% of patients with sarcoidosis. However, measurement of serum ACE levels lacks sensitivity and specificity[54]. sIL-2R, released by activated T cells, predict ^{18}F-fluorodeoxyglucose positron-emission tomography (^{18}F-FDG-PET) uptake, but they do not have a 100% sensitivity[55]. sIL-2R and lysozyme are promising markers with respect to lymphocytic alveolitis[56]. The maximum serum lysozyme levels has a tendency to increase significantly with the number of organs involved, however, serum lysozyme is much less specific for sarcoidosis than serum ACE[57].

Biopsy

In the presence of a compatible clinical picture, the first step is to choose the site for a proper biopsy[46]. The diagnostic yield of transbronchial lung biopsy (TBLB) ranges from 40% to more than 90% when four to five lung biopsies are performed[58]. Studies of bronchoalveolar lavage (BAL) with lymphocyte subpopulations are sometimes helpful. A CD4/CD8 ratio > 3.5 provides a diagnosis of sarcoidosis with a specificity of 94%, even if the TBLB has not been diagnostic[59]. In patients without biopsy specimens, diagnosis may be performed by clinical and/or radiological features alone with Stage Ⅰ (reliability of 98%), Stage Ⅱ (89%), Stage Ⅲ (52%), and Stage 0 (23%) disease[60].

Positron-emission tomography

^{18}F-FDG-PET is a well-established functional imaging technique for diagnosing cancer because it can detect increased glucose metabolism in the lesion[61]. It is also used for detecting high glucose metabolism in infectious diseases and fevers of unknown origin[62-64]. High uptake of ^{18}F-FDG has also been reported in patients with sarcoidosis[65-68]. It is proposed that inflammatory cells such as neutrophils, lymphocytes, and activated macrophages at the site of inflammation or infection are responsible for the accumulation of ^{18}F-FDG[69-72]. FDG-PET/CT is useful for evaluating the extent of sarcoidosis and recognizing lesions at different sites, including lymph nodes, liver, spleen, and bone[73].

The majority of sarcoidosis patients with persistent disabling symptoms had FDG-PET positive findings and remarkably, 80% of the lesions were extra-thoracic. FDG-PET appeared to be of additional value to assess inflammatory activity and to detect extra-thoracic lesions[74]. FDG-PET proved advantageous for determining the spread of active disease throughout the body and positive results were significantly associated with changes in therapy[75]. FDG-PET is also useful for detecting cardiac involvement in sarcoidosis[76,77]. Although the frequency of right ventricular (RV) involvement was lower than that of left ventricular (LV) involvement[78,79], ^{18}F-FDG RV uptake may be useful in diagnosing cardiac involvement in sarcoidosis[80]. Long fasting is effective in inhibiting myocardial ^{18}F-FDG uptake, and appropriate diets can enable the detection of active cardiac sarcoidosis lesions with FDG-PET images[77,81,82].

FDG-PET/CT may be helpful in the diagnosis of sarcoidosis, however, the high cost does not allow wide application. Active granulomatous disease, infectious disorders, and other non-infectious inflammatory conditions or proliferative disorders demonstrate varying degrees of ^{18}F-FDG uptake on PET scans due to an inflammatory reactive response[72].

It is difficult to differentiate tuberculosis from sarcoidosis, however, the promising features of FDG-PET imaging in the management of patients with tuberculosis are its potential role for assessing therapeutic response, its ability to detect unsuspected distant sites of infection, its role in guiding biopsies, and diagnosis of suspected recurrence and residual disease. The pattern of FDG-PET images in both sarcoidosis and lymphomas is non-specific and also cannot be differentiated[72].

Endobronchial ultrasonography

The usefulness of endobronchial ultrasonography (EBUS)-guided transbronchial needle aspiration (TBNA) in the diagnosis and staging of lung cancer is widely recognized. However, its importance in the diagnosis of benign pathology of the chest, including sarcoidosis, is progressively increasing. In the absence of easily accessible biopsy sites (skin or superficial lymph nodes), flexible bronchoscopy with TBLBs is recommended[83]. TBLB, however, has moderate sensitivity (60%) to detect granulomas even when combined with endobronchial biopsies[84-86]. A diagnostic yield of 80%-82% with EBUS-TBNA for detection of granulomas has been reported in patients with suspected sarcoidosis[87,88].

Recent data from randomized trials have demonstrated the superiority of EBUS-TBNA to conventional TBNA[89,90] and bronchial and transbronchial biopsies[87,91] for the diagnosis of pulmonary sarcoidosis. The addition of TBLB significantly enhanced the yield of EBUS-TBNA[92,93]. EBUS-TBNA is a safe and highly effective technique in patients with mediastinal and hilar lymphadenopathy and can prevent the need for 87% of mediastinoscopies[94].

A prospective study conducted in patients with

suspected stage Ⅰ and Ⅱ pulmonary sarcoidosis demonstrated that 84.6% of patients who underwent EBUS-TBNA had a definitive diagnosis of sarcoidosis, and 93.9% of these patients were confirmed to have non-caseating epithelioid cell granuloma. The sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of EBUS-TBNA was 93.9%, 100%, 100%, 75.0% and 94.8%, respectively[95].

It is sometimes difficult to distinguish between a malignant lymph node and lymphadenopathy due to sarcoidosis. Homogeneous low echogenicity and the presence of a germinal center structure of lymph nodes were observed in sarcoidosis more frequently than in lung cancer, and that may help to distinguish sarcoidosis from lung cancer[96].

DIAGNOSTIC CRITERIA AND ORGAN INVOLVEMENT

Clinical manifestations may vary, but a diagnosis of sarcoidosis requires the presence of granulomatous inflammation in at least two organs[47,97]. Japanese diagnostic criteria are based on the clinical manifestation, radiological findings, serum or urine markers, histological findings, and the exclusion of other diseases, compatible with previously reported diagnostic criteria[46,98-102]. Sarcoidal granulomas can involve any organ, but in more than 90% of patients, clinical sarcoidosis manifests with skin, and ocular signs and intrathoracic or pulmonary involvement. In the new sarcoidosis organ assessment instrument developed by the World Association of Sarcoidosis and Other Granulomatous Diseases (WASOG), clinical manifestations of 16 organs were assessed as either: (1) highly probable: likelihood of sarcoidosis at least 90%; (2) probable: likelihood of sarcoidosis between 50% and 90%; and (3) possible: likelihood of sarcoidosis less than 50%[103]. The prevalence of each finding differs by country, therefore, a diagnosis of sarcoidosis should be made with consideration of the epidemiology and varying clinical characteristics in each country.

Pulmonary sarcoidosis

Pulmonary sarcoidosis is the most common clinical manifestation, with a prevalence of 95% in Caucasian and black[104], and 86% in Japanese patients[4]. Bilateral hilar lymphadenopathy of chest radiography is "highly probable", and lymphocytic alveolitis, an elevated CD4/CD8 ratio, and lymphoid aggregates/giant cells on bronchoscopy are "probable" findings[103], compatible with the Japanese criteria. Chronic beryllium disease, pneumoconiosis, tuberculosis, malignant lymphoma, hypersensitivity pneumonitis, Wegener granulomatosis, metastatic lung cancer, amyloidosis should be differentiated from pulmonary sarcoidosis.

Ocular sarcoidosis

Ocular lesions are common among patients with sarcoidosis, with a reported incidence of 11%-83% during the disease course[83,105], and 1.5%-12.4% at first presentation[106-108]. In Japan, an ocular lesion is the most common presentation of sarcoidosis with an incidence of 54.8%, compared with 11.8% in Caucasian and black patients[104], and it has recently increased[4]. In Japanese new guidelines for the diagnosis of ocular sarcoidosis[109], cases meeting 2 or more of the 6 categories are diagnosed with clinically suspected ocular sarcoidosis, and subjected to tests of the diagnostic criteria of sarcoidosis (Table 1). The new guidelines achieved more than 80% specificity for all categories, and positive and negative predictive values and the likelihood ratios for a positive and negative test result improved, compared with old guidelines[109]. Granulomatous anterior uveitis, muton-fat keratic precipitates, iris nodules, and snowball/string of pearls are "highly probable" manifestations of ocular sarcoidosis[103] and are also included in the Japanese criteria. Even in patients with suspected ocular sarcoidosis without lung field involvement, lymphocyte counts in bronchialveolar lavage were significantly elevated, and prednisolone must be administered to prevent loss of vision in such patients[110]. Tuberculosis, herpes simplex uveitis, uveitis associated with human T cell leukemia virus (HTLV)-1, Posner-Schlossman Syndrome, Behçet's disease, and malignant lymphoma should be differentiated from ocular sarcoidosis.

Cardiac sarcoidosis

The prevalence of cardiac sarcoidosis is lower than pulmonary, cutaneous, or ocular sarcoidosis, however, the diagnosis of cardiac sarcoidosis is important because it is found to be the main cause of death at autopsy in Japan[111,112]. The incidence of cardiac sarcoidosis in Japan is reported to be 23%[4], much higher than the 2.3% cited in the ACCESS study[104]. Although sarcoidosis is generally associated with a low mortality rate, concomitant cardiac involvement worsens its prognosis[113,114]. Therefore, detection of myocardial involvement is critical for the management of patients with sarcoidosis. There are several "probable" manifestations for cardiac sarcoidosis, such as reduced left ventricular ejection fraction, advanced atrioventricular block, and positive gallium uptake; however, no "highly probable" manifestations have been reported[103].

In 2006, the Japanese Society of Sarcoidosis and Other Granulomatous Disorders revised the original guidelines of the Japanese Ministry of Health and Welfare for diagnosing cardiac sarcoidosis[115]. In these revised guidelines[116], the histological diagnosis of cardiac sarcoidosis is confirmed when myocardial biopsy specimens demonstrate non-caseating epithelioid cell granulomas with histological or clinical diagnosis of extracardiac sarcoidosis. Clinical cardiac sarcoidosis is diagnosed in the absence of an myocardial biopsy specimen or in the absence of typical granulomas on myocardiac biopsy when extracardiac sarcoidosis has

Table 1 Guidelines for diagnosis of ocular sarcoidosis

Infiltrates in anterior chamber: granulomatous (mutton-fat keratic precipitates/iris nodules)
Trabecular meshwork nodules and/or tent-shaped peripheral anterior synechiae
A mass of vitreous opacities (snowball or string of pearls-like appearance)
Retinal perivasculitis (mainly periphlebitis) with perivascular nodules
Multiple candle-wax type chorioretinal exudates and nodules and/or laser photocoagulation spots-like chorioretinal atrophy
Optic disc nodule(s)/granuloma(s) and/or solitary choroidal nodule

been diagnosed histologically or clinically[116]. Basal thinning of the interventricular septum is an important finding for diagnosing cardiac sarcoidosis. Giant cell myocarditis should be excluded when diagnosing cardiac sarcoidosis. These guidelines are useful, particularly in patients with subclinical cardiac sarcoidosis and proven noncardiac sarcoidosis. This is simple translation of cardiac features of sarcoidosis and details of these Japanese guidelines would be updated in near future. However, there are no currently accepted international guidelines for the diagnosis of cardiac sarcoidosis. Expert consensus recommendations on criteria was reported to establish working criteria for the diagnosis of cardiac sarcoidosis on the basis of expert opinion and the limited available data, and there are two pathways to a diagnosis of cardiac sarcoidosis: histological and clinical diagnosis (Table 2)[117]. Guidelines for the diagnosis of cardiac sarcoidosis are going on evolution with international standpoint. As regard, there are both concepts of isolated cardiac sarcoidosis, and of a part of the systemic disease.

Cutaneous sarcoidosis

Skin involvement is common and occurs in approximately 15%-25% of patients with sarcoidosis[104,118]. Two clinically important and easily recognizable skin lesions are erythema nodosum and lupus pernio. Lupus pernio is the only "highly probable" cutaneous manifestation of sarcoidosis[101]. In Japan, the incidence of erythema nodosa and lupus pernio is 6.2% and 2.6% respectively. These conditions are rare in Japan compared with other countries[4,46].

Other extrathoracic sardoicosis

Extrathoracic manifestations, usually associated with thoracic involvement, are seen in 25%-50% of cases[47]. Some sarcoidosis patients have disabling nonspecific symptoms such as fatigue and pain. It has been reported that sarcoidosis patients with unexplained pain or autonomic dysfunction had reduced intraepidermal nerve fiber density, therefore some patients with sarcoidosis may have small fiber neuropathy with autonomic involvement to explain nonspecific symptoms[119]. In Japan, evaluation of non-caseating epithelioid cell granulomas or clinical manifestations in other organs is needed, in addition to the diagnosis of sarcoidosis in one organ, to diagnose extrathoracic sarcoidosis.

TREATMENT-POTENTIAL TREATMENT STRATEGIES ON THE BASIS OF DISEASE CAUSE

Immunosuppressive agents, mainly corticosteroids, have been used for treating sarcoidosis for more than 50 years. It is undoubtedly true that many subjects benefit from the use of corticosteroids. However, the long-term effects of steroid treatment for chronic sarcoidosis remain controversial, and the side effects of long-term use often represent a clinical challenge. In fact, only a few randomized controlled trials have been conducted on the use of corticosteroids[120-123].

On the basis of the hypothesis that sarcoidosis represents an aberrant immune response to infectious agents, as described above, eradication of the causative bacterium with antibiotics has been considered a potentially attractive strategy to achieve cure. In an observational study, Bachelez *et al*[124] reported the possible benefits of tetracyclines, to which *P. acnes* is sensitive, for the treatment of chronic forms of cutaneous sarcoidosis. Case reports describing the efficacy of minocycline and/or clarithromycin against multiple endobronchial mass lesions[125] and muscular lesions[126] of sarcoidosis have also been reported from Japan. Furthermore, the results of a nationwide questionnaire survey conducted in Japan in 2005 and reported in Japanese indicated that antibiotic therapy was effective in 43% of 87 patients with sarcoidosis. The patients were treated using a variety of antibiotics including minocycline, doxycycline, and clarithromycin. Considering the heterogeneous pathogenesis of the disease, not all subjects would be expected to show a response to antibiotics. Rather, clarification of phenotypes in relation to the effectiveness of antibiotics, and clinical trials targeting potentially responsive phenotypes, are warranted to establish the efficacy of antibiotics to treat sarcoidosis.

PROGNOSIS

The prognosis of patients with sarcoidosis mainly depends on the extent and severity of the systemic involvement[127-130], however, ethnic, geographic, social, and economic variations affect the clinical course[1,46,131,132]. Sarcoidosis patients commonly have spontaneous remission and nearly two-thirds of patients

Table 2 Expert consensus recommendations on criteria for the diagnosis of cardiac sarcoidosis

Histological diagnosis from myocardial tissue
Cardiac sarcoidosis is diagnosed in the presence of non-caseating granuloma on histological examination of myocardial tissue with no alternative cause identified (including negative organismal stains if applicable)
Clinical Diagnosis from Invasive and Non-Invasive Studies:
There is a histological diagnosis of extra-cardiac sarcoidosis
and
One or more of following is present
Steroid ± immunosuppressant responsive cardiomyopathy or heart block
Unexplained reduced left ventricular ejection fraction (< 40%)
Unexplained sustained (spontaneous or induced) ventricular tachycardia
Mobitz type II 2nd degree heart block or 3rd degree heart block
Patchy uptake on dedicated cardiac PET (in a pattern consistent with cardiac sarcoidosis)
Late Gadolinium Enhancement on cardiovascular magnetic resonance (in a pattern consistent with cardiac sarcoidosis)
Positive gallium uptake (in a pattern consistent with cardiac sarcoidosis)
Other causes for the cardiac manifestation(s) have been reasonably excluded

PET: Positron-emission tomography.

have a good prognosis.

Löfgren's syndrome is associated with a good prognosis[133], typically with HLA-DRB1*0301[48,49]. Other gene variants also have suggested associations with sarcoidosis. HLA-A1, -B8, DQB1*0201, and Arg74 in DRB1 pocket 4 are associated with a good prognosis[52,53]; HLA-A3, -B7, DRB1*1401, DRB1*1501, DQB1*0602, DRAla71, and DQTyr30 with prolonged disease[50,51]; DRB1*0401 with eye sarcoidosis[134]; and DQB1*0601 with cardiac sarcoidosis[135]. BTNL2 rs2076530SNP was associated with susceptibility to develop sarcoidosis, but not with an increased risk of cancer in sarcoidosis patients[136]. Genetic association has also been estimated for organ involvement, which is highly associated with prognosis of sarcoidosis[47,50-53]. However, the actual pathogenetic mechanisms of certain genes remains under investigation. Further studies are needed to elucidate potential genetic factors associated with specific endotypes of sarcoidosis.

Some patients (10%-30%) show chronic, progressive, and life-threatening conditions[137-144]. Serious extrapulmonary involvement occurs in 4%-7% of patients with sarcoidosis at presentation[137-139,145-148].

With regard to ethnic differences in disease severity, sarcoidosis in blacks is more severe, and Caucasians are more likely to present with asymptomatic disease according to the general consensus from the review of a large series of cases[47]. The development of new organ involvement over the 2-year follow-up period was more common in blacks compared to Caucasians[149]. Blacks tend to have a higher incidence of chronic progressive pulmonary disease, extrapulmonary involvement, and lupus pernio with a worse prognosis[149].

In Japan, cardiac involvement is the main cause of mortality, accounting for 77% of sarcoidosis deaths[150]. However, in western countries, most fatalities from sarcoidosis are due to advanced pulmonary fibrosis rather than cardiac involvement[46]. Cardiac sarcoidosis is one of the important prognostic factors, accounting for up to 25% of disease-associated mortality due primarily to either progressive heart failure or cardiac arrhythmias[151]. In a study of necropsy cases[69], sudden death was the initial manifestation of sarcoidosis in 35%, presumably due to arrhythmias. The incidence of cardiac sarcoid granuloma in Japanese was significantly higher than that seen in Caucasians and blacks, and Japanese showed the highest rate of cardiac sarcoid-related deaths[152]. Cardiac sarcoidosis has been reported to have a much worse prognosis than idiopathic dilated cardiomyopathy in Japanese patients[153].

Chest radiographic staging (0, Ⅰ, Ⅱ, Ⅲ, Ⅳ) has been correlated with the disease course, with the worse prognosis in patients with higher chest radiographic stages. The prognosis of pulmonary sarcoidosis, defined as the normalization rate of chest radiographs, was significantly better in Japanese than that in Finnish patients[154]. In a study of prognosis of sarcoidosis, autopsy cases were reviewed. Approximately 80%-90% of Stage Ⅰ or Ⅱ patients showed spontaneous remission, the prognosis of Stage Ⅲ patients was poor and corticosteroid therapy seemed to be ineffective[155]. Patients with a predominantly ground-glass opacity and consolidation pattern on the initial high-resolution computed tomography (HRCT) scan had a worse prognosis. HRCT scan may be helpful in predicting the outcomes of patients with sarcoidosis[156].

Some types of specific cutaneous lesions have prognostic significance that may help to predict the outcome of the systemic disease. Skin plaques and lupus pernio, for example, are associated with chronic sarcoidosis[157,158]. In a study of the prognosis of cutaneous sarcoidosis, erythema nodosum was the best prognostic indicator of systemic disease[159,160]; however, a good prognosis for sarcoidosis patients with erythema nodosum was limited to Caucasian patients[128].

Pulmonary hypertension (PH), a well-recognized complication of sarcoidosis with a prevalence not exceeding 5%[145,161-163], is known to have an extremely poor prognosis in patients with sarcoidosis[139,164].

Survival in sarcoidosis patients with PH was significantly worse than in controls without PH, and PH was the cause of 57.1% of deaths[165]. In a retrospective review of sarcoidosis patients with PH, targeted therapies (phosphodiesterase-5 inhibitors, endothelin receptor antagonists, or combinations) were reported to be safe[166]. Further studies are needed to establish effective therapies for PH.

Other adverse prognostic factors are advanced age at onset, the presence of symptoms, extrathoracic involvement, treatment with corticosteroids[167], severe dysfunction on pulmonary function tests[168], increased neutrophil count in broncho-alveolar lavage fluid[169,170], and misdiagnosis of sarcoidosis in patients with granulomatous and lymphocytic interstitial lung disease[171].

FUTURE DIRECTIONS

Although numerous sarcoidosis studies have been conducted over the past decade, the etiology remains unknown and some patients die due to severe disease associated with cardiac involvement or pulmonary fibrosis. Further studies are needed to determine the cause of sarcoidosis; elucidate the risk factors for progressive disease; and identify new and effective treatments through establishing international communication and evaluation. This research may improve our management of sarcoidosis.

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