Respiratory Medicine (2015) 109, 272–278

Available online at www.sciencedirect.com

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journal homepage: www.elsevier.com/locate/rmed

Age-related and historical changes in the clinical characteristics of sarcoidosis in Japan

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Received 3 May 2014; accepted 26 December 2014
Available online 3 January 2015

KEYWORDS
Age;
Epidemiology;
Sarcoidosis;
Race;
Sex

Summary
Background: National surveys conducted in Japan between 1960 and 2004 suggest a gradually increasing incidence of sarcoidosis in women >50 years old with increased involvement of the eye, skin, and heart. However, whether this involvement is due to the increased age at diagnosis is still unclear. We aimed here to identify the age-related differences in organ involvement in sarcoidosis in Japan, as well as the historical changes in clinical characteristics and the age-specific distribution of cases at diagnosis.
Methods: We reviewed 588 consecutive Japanese patients newly diagnosed with sarcoidosis between 1974 and 2012 at Jichi Medical University Hospital. We compared organ involvement between subgroups differentiated by sex and age (<45 years; n = 275; ≥45 years; n = 313) at diagnosis and identified historical changes in the age-specific distribution in 10-year intervals.
Results: Younger patients had more common involvement of extrathoracic lymph nodes, parotid/salivary gland, and liver, while older patients had more common involvement of non-lymphatic extrathoracic organs such as the eye, heart, muscle, and kidney. The age at diagnosis has consistently increased over the past four decades. The monophasic distribution in

Abbreviations: BHL, bilateral hilar lymphadenopathy; JSSOG, Japanese Society of Sarcoidosis and Other Granulomatous Disorders; WASOG, World Association of Sarcoidosis and Other Granulomatous Disorders; Th1, T helper 1 cell; ACCESS, A Case Control Etiologic Study of Sarcoidosis.

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http://dx.doi.org/10.1016/j.rmed.2014.12.012

men has tended to become biphasic, and the biphasic distribution in women monophasic. Increasing trends were apparent for hypercalcemia and involvement of the gastrointestinal tract, skin, nervous system, muscle, and kidney.
Conclusions: Elderly patients at diagnosis had various extrathoracic involvement including eye, skin, and cardiac lesions. Moreover, the age at diagnosis of sarcoidosis has continued to increase in both sexes, influencing the recent trends in clinical characteristics.

Introduction

Sarcoidosis is a granulomatous disease of unknown etiology with heterochronic involvement of various organs. It generally develops in adults younger than 40 years of age, with incidence peaking at 20 and 29 years [1]. In Japan, as well as in European countries, the age-specific incidence in women is biphasic, with a second peak after 50 years of age [2,3]. However, there is some evidence of an upward shift in age at diagnosis over time in the United States and Denmark [4—6]. In Japan, the results of 9 national epidemiological surveys conducted between 1960 and 2004, albeit in different study settings, also suggested a gradual increase in the incidence of sarcoidosis in women after 50 years of age [3]. The occurrence of bilateral hilar lymphadenopathy (BHL) and incidental detection on chest radiography have decreased, while at the same time the occurrence of eye, skin, and cardiac involvement has increased [3]. A previous single-institution observation by another group also revealed increasing trends in extrathoracic involvement since the 1980s [7,8]. It remains unclear whether or not these trends in the clinical characteristics of sarcoidosis arise from increasing age at the time of diagnosis.

In a recent study, we showed that the proportion of patients in Japan with stage 1 or 2 sarcoidosis, which reflects patients presenting with BHL, decreased consistently with increasing age [9]. However, age-related differences with regard to specific organ involvement have yet to be determined. Against this background, we aimed in the present study to identify the age-related differences in organ involvement in Japan, as well as determine the historical changes over the past four decades in the age-specific distribution of cases at diagnosis. In addition, we examined whether these results are compatible with the aforementioned recent trends in clinical characteristics.

Methods

Study population

We retrospectively reviewed the medical records of 588 consecutive patients newly diagnosed with sarcoidosis (431 biopsy-proven, and 157 clinically proven) who were admitted to or underwent bronchoscopy at Jichi Medical University Hospital between April 1974 and July 2012. The subjects were the same as those included in our previous study [9]. Diagnosis was made based on the "Diagnostic Criteria and Guidelines for Sarcoidosis" developed by the Japanese Society of Sarcoidosis and Other Granulomatous Disorders (JSSOG 2007) [10]. This study was reviewed and approved by the Jichi Medical University Institutional Review Board (No. Rin-A12-54, January 8, 2013).

JSSOG 2007 Diagnostic Criteria and Guidelines for Sarcoidosis

These criteria concern biopsy-proven and clinically proven diagnosis. They are in agreement with the concepts of the American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) statement on sarcoidosis adopted in 1999 [1], which detail the clinical features of sarcoidosis, including radiological, laboratory, and pathological findings (noncaseous epithelioid cell granuloma), and differential diagnoses. Clinically proven diagnosis with no histological evidence is made based on the following two points: (1) clinical features suggesting sarcoidosis-like lesions in 2 or more organs, (2) 2 or more clinical features suggesting a systemic reaction, such as BHL, elevated serum angiotensin-converting enzyme, hypercalcemia, negative tuberculin test, abnormal uptake on gallium-67 citrate scintigraphy, elevated lymphocyte count, and elevated CD4/CD8 ratio in bronchoalveolar lavage fluid.

Organ involvement assessment

Organ involvement at the time of diagnosis was retrospectively determined in each patient using the aforementioned JSSOG 2007 criteria [10] based on case history, physical examination, and clinical findings, including imaging abnormalities. Even without the grading system, these criteria are as detailed as the recent WASOG sarcoidosis organ assessment instrument [11]. For example, clinical features suggesting sarcoidosis-like lesions in the liver include abnormal findings such as hepatic nodules and hepatomegaly detected by laparoscopy, ultrasonography, computed tomography, and magnetic resonance imaging, as well as liver dysfunction. Diagnostic imaging to detect lung involvement ranged from radiology to bronchoscopy. Hypercalcemia was determined from the laboratory findings noted closest to the time of diagnosis during admission.

Statistical analysis

Comparisons between subgroups differentiated by sex and age at diagnosis (younger diagnosis group, <45 years of age; and older diagnosis group, ≥ 45 years of age) were