Clinic Rev Allerg Immunol (2015) 49:1–5
DOI 10.1007/s12016-015-8480-0

Sarcoidosis: a Critical Review of History and Milestones

Paolo Spagnolo

Published online: 4 March 2015

Abstract Sarcoidosis is a chronic systemic disease of unknown origin and uncertain prognosis that most commonly affects young adults, and frequently presents with bilateral hilar lymphadenopathy, pulmonary infiltrates and ocular and skin lesions. The diagnosis is established when characteristic clinical-radiological features are supported by compatible histopathology of epithelioid cell granulomas, following exclusion of known causes of granulomatous inflammation. Indeed, sarcoidosis belongs to a large family of disorders that share granuloma formation as common denominator. Since its first description by Jonathan Hutchinson in 1869, sarcoidosis has generated enormous interest and considerable controversy. In Hutchinson's day, it was considered a dermatological condition, which gradually evolved into a multisystem disorder associated in the majority of cases with respiratory abnormalities. With time, it has also become clear that sarcoidosis occurs throughout the world, affecting individuals of both genders and all races, although its prevalence varies widely across ethnic and racial groups. In recent years, advances in different disciplines, particularly biochemistry, genetics, immunology and molecular biology, have improved dramatically our understanding of the disease. Yet, the critical questions regarding who gets sarcoidosis and whether it has an infectious origin remain unanswered. Sarcoidosis has a distinguished medical history that covers the last 150 years. Right from the time of seminal contributions by Hutchinson, Besnier and Boeck medical discussion on sarcoidosis has always been animated and to a certain extent emotional. Such discussions will inevitable continue until the true cause of the disease has been found, hopefully in the near future.

Keywords Sarcoidosis · History · Milestones · Initial description · Cause

Preface

> When a thing ceases to be a subject of controversy, it ceases to be a subject of interest (William Hazlitt).

Historical Overview and Milestones

Jonathan Hutchinson and Mortimer's Malady The first clinical description of sarcoidosis dates back to 1869 and refers to a 58-year-old coal-wharf worker who visited Jonathan Hutchinson—one of the most distinguished medical consultants of all times—at the Blackfriars Hospital for Diseases of the Skin of London. This patient complained of purple, symmetrical skin plaques on his legs and hands that had gradually developed over the preceding 2 years. Hutchinson described the lesions, which were neither tender nor painful, as livid papillary psoriasis and considered them somehow related to the patient's gout [1]. Another Hutchinson's patient was a 64-year-old lady, Mrs Mortimer, who presented with raised, red skin lesions on her face and forearms which increased in size and extent over the following 6 months. The skin lesions differed from both tuberculosis and lupus; therefore, he decided to label the condition "Mortimer's malady" after the patient's name [2].

P. Spagnolo (✉)
Medical University Clinic, Canton Hospital Baselland and University of Basel, Rheinstrasse 26, 4410 Liestal, Switzerland
e-mail: paolo.spagnolo@ksbl.ch

From a Dermatological Condition to a Systemic Disease In 1889, Ernest Besnier, a French dermatologist, coined the term "lupus pernio" to describe a patient with purplish swellings of the nose, ears and fingers [3]. Ten years later, Caeser Boeck, a Norwegian dermatologist, presented to the Medical Society of Christiania a patient with "multiple benign sarkoid of the skin" and emphasized its similarity to the Mortimer's malady. Boeck, who coined the term "sarkoid" because the lesions resembled sarcoma, was also the first to describe the granulomatous histology of sarcoidosis. Just before his death, Boeck published a large series of 24 cases of "benign miliary lupoids", some of which showed involvement of the lungs, conjunctiva, bone, lymph nodes, spleen and nasal membrane [4]. The multi-organ nature of the disease was starting to emerge. Over the following few years, Christian Frederick Heerfordt, a Danish ophthalmologist, described a syndrome characterized by cutaneous lesions, uveitis, enlargement of the parotid and submaxillary salivary glands and paresis of the cranial nerves (especially the seventh nerve) and termed it "febris uveo-parotidea subchronica" [5]. After it had been demonstrated that sarcoidosis encompassed a broad range of clinical manifestations with involvement of many different organ systems, Jörgen Nilsen Schaumann, a Swedish dermatologist, provided a common pathologic basis for the diverse clinical aspects of the disease and called it "lymphogranuloma benigna" to emphasize its systemic nature [6]. Finally, in 1946, Sven Löfgren, a Swedish physician, described a syndrome consisting of fever, bilateral hilar lymphadenopathy, polyarthritis and erythema nodosum that is now known as Löfgren's syndrome [7].

The Kveim Test In 1941, Ansgar Kveim, a Norwegian dermatologist, made the observation that intradermal injection of a crude homogenate of sarcoid tissue produced, over several weeks, papules containing epithelioid cell granulomas in individuals with sarcoidosis but not in control subjects, including some with tuberculosis [8]. Louis Siltzbach, whose name is often appended to that of Kveim in the eponym, significantly contributed to the purification of the particulate suspensions and standardization of the test [9]. Despite major advances in our knowledge of disease pathology and diagnosis, basic questions about the Kveim response remain unanswered, most importantly the nature of the "Kveim antigen".

Disease Overview

Initially, sarcoidosis was considered a dermatologic condition (the common involvement of the lungs was not apparent until the availability of chest roentgenogram), and it was only with time that the disease revealed its protean clinical manifestations and multisystem nature. Indeed, although the lung is a predominant site of involvement in the majority of cases, sarcoidosis may affect virtually any organ. As such, it is a disorder that multiple medical subspecialists can come across in their clinical practice.

The development and accumulation of (non-caseating) granulomas—discrete, compact collections of macrophages, epithelioid cells and $CD4^+$ lymphocytes—represent the histologic hallmark of sarcoidosis, although they are not specific for the disease (Table 1, Fig. 1).

According to the most simplistic hypothesis, granulomas form in response to pathogens, limit inflammation and protect surrounding tissue. Yet, in sarcoidosis, persistent granulomatous inflammation leads to distortion of local architecture, tissue injury and, in severe cases, irreversible fibrosis. Recent advances in immunology, genetics and molecular biology have substantially increased our understanding of the complexity of the disease. From an earlier concept of sarcoidosis being an immunodeficiency disorder, there is now consensus that sarcoidosis results from exposure of genetically susceptible hosts to—as yet unidentified—environmental agents that trigger a Th1-type cellular immune response with granuloma formation. The lungs, eyes and

Table 1 Major pathologic differential diagnosis of sarcoidosis

Infections	Bacteria, chlamydia, fungi, metazoa, mycobacteria (*M. tuberculosis* and atypical mycobacteria), protozoa, rickettsia, spirochaetes, viruses
Vasculitis	Bronchocentric granulomatosis, Churg-Strauss syndrome, granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis), necrotizing sarcoid granulomatosis
Organic agents (hypersensitivity pneumonitis)	Farmers' lung, bird fanciers' lung
Inorganic agents (pneumoconiosis)	Aluminium, beryllium, silica, talc, titanium, zirconium
Immunuological disorders	Blau's syndrome, Crohn's disease, hypogammaglobulinaemia, Langerhans cell histiocytosis, primary biliary cirrhosis
Malignancy	Carcinoma, Hodgkin's disease, non-Hodgkin's lymphoma
Drug reactions	
Aspiration of foreign materials	
Miscellaneous	Granulomatous histiocytic necrotizing lymphadenitis (Kikuchi-Fujimoto disease), granulomatous lesions of unknown significance (GLUS syndrome)

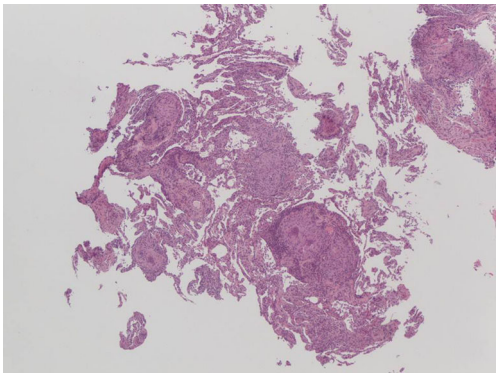

Fig. 1 Sarcoidosis. Transbronchial lung biopsy specimen showing non-caseating granulomatous inflammation with lymphangitic distribution, haematoxylin-eosin (40×). Courtesy Giulio Rossi (Modena, Italy)

skin, all common targets for sarcoidosis, are regularly in contact with environmental agents, and several studies of sarcoidosis immunopathogenesis suggest that the disease results from an exuberant response to airborne antigens [10–14]. Yet, the aetiology of sarcoidosis remains unknown and its pathogenesis incompletely understood. This failure speaks to the complexity of the problem from both an exposure and genetic perspective. In addition, there is no definitive diagnostic blood, skin or radiologic imaging test specific for the disorder. Accordingly, the diagnosis requires a combination of (a) compatible clinical-radiological findings, (b) histological evidence of non-caseating epithelioid granulomas at disease sites and (c) exclusion of known causes of granulomatous inflammation and local sarcoid-like reactions [15], Table 1).

Sarcoidosis affects most commonly young and middle-aged individuals of both genders and all races. Although extensively studied, its exact incidence and prevalence are difficult to estimate, mostly due to unrecognized and undiagnosed cases, lack of consistent case definition, variable methods of case ascertainment, variability in disease presentation and presence in some geographic areas of other more commonly recognized granulomatous diseases (e.g. tuberculosis, leprosy, fungal infection) that obscure sarcoidosis recognition. Sarcoidosis has been reported in all racial and ethnic groups. Yet, it affects Afro-Caribbeans and African-Americans more commonly and more severely than people of other races, whereas Caucasians tend to present with asymptomatic and chronic disease [16]. While some of the differences observed across racial and ethnic groups may be attributed to under- or overdiagnosis, to a greater degree, these differences probably reflect differences in genetic susceptibility related to varied genetic backgrounds. The clinical presentation of sarcoidosis has important implications for prognosis, with an acute onset of fever, bilateral hilar lymphadenopathy and erythema nodosum (Löfgren's syndrome, Fig. 2) being associated almost invariably with a self-limited course and resolution—either spontaneously or with treatment—whereas a more insidious onset is often followed by a more chronic course (Fig. 3). On the other hand, features of sarcoidosis such as lupus pernio (the most

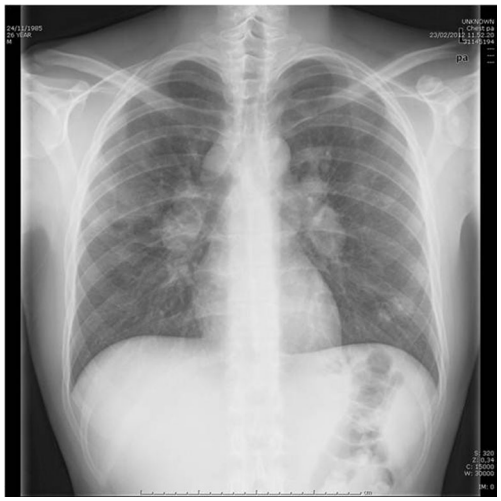

Fig. 2 Sarcoidosis. Radiographic stage I disease. Standard postero-anterior chest radiograph in a 26-year-old man shows bilateral hilar and mediastinal lymph node enlargement without parenchymal disease

characteristic sarcoid skin lesion), neurologic involvement, bone cysts and pulmonary fibrosis are predictive of a more chronic course and low rate of remission. Whether these differing disease phenotypes and dichotomy in prognosis reflect differing immunologic pathways is unknown.

The extreme variability in clinical presentation and disease behaviour raises the possibility that sarcoidosis (a) might not be a single disease, (b) might be triggered by more than one etiologic agent, or (c) that a single agent might produce a range of clinical manifestations based on host factors (e.g. genetics). If sarcoidosis, as many believe, is a heterogeneous collection of disorders, refining the phenotype is crucial. For example, there is convincing evidence suggesting that Löfgren's syndrome is a separate disease based on its genetics, immunology, clinical phenotype and behaviour [17, 18]. By

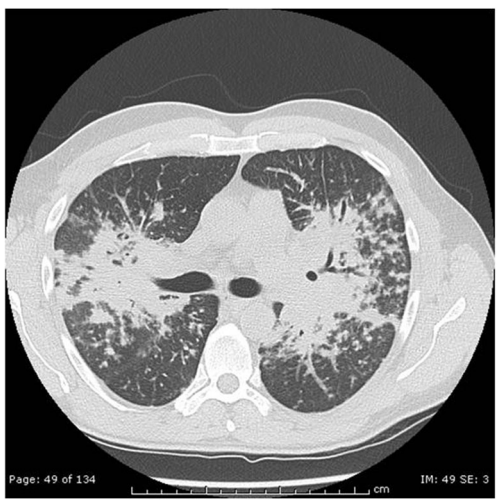

Fig. 3 Pulmonary sarcoidosis. High-resolution computed tomography of the chest in a 52-year-old man shows a classical combination of hilar and mediastinal lymphadenopathy, perilymphatic nodules, bronchovascular and interlobular septal beading and centrilobular and subpleural nodules

purifying the clinical phenotype, thus reducing disease heterogeneity, it will be easier to examine possible environmental causes of each of these separate conditions [19]. The concept that various genetic and environmental factors are likely involved in disease aetiology is corroborated by the non-uniform incidence of the disease across ethnicities together with the observed familiar clustering. A required interplay between specific combinations of exposures and host responses in the pathogenesis of sarcoidosis would also explain why so many studies have come to conflicting conclusions with regard to the aetiology of the disease [20]. Yet, the primary cause of sarcoidosis may be an intrinsic aberrant immunologic responsiveness of the host to several exposures rather than the exposures per se. These pathogenetic hypotheses are not mutually exclusive.

Since its first description, sarcoidosis has generated enormous interest and extraordinary controversy mainly related to its origin, variable presentation and unpredictable clinical course. While no specific answers have been provided in this regard, our knowledge of the disease has greatly improved, and this issue summarizes much of it. Sarcoidosis is a systemic disease resulting from a specific immune reaction that is triggered by one or more agents and modified by host/genetic factors. Drs. Chen and Moller provide a comprehensive review of the possible infectious and non-infectious causes of sarcoidosis. The immune response of sarcoidosis, which culminates in granuloma formation, is strongly Th-1 polarized. Yet, its modification may contribute to the variability of the outcome. Sarcoidosis develops in genetically predisposed individuals, but genetics is also likely to contribute to the wide variety of clinical presentation, progression and prognosis observed in this disease. These issues are summarized by Dr. Grunewald and colleagues. Sarcoidosis is diagnosed based on compatible clinical and radiologic findings supported by histologic evidence of non-caseating epithelioid-cell granulomas in one or more organs in the absence of organisms or particles. However, the diagnosis is one of exclusion, and differential diagnosis is often problematic. This topic is addressed by Dr. Wessendorf and colleagues. There are no histologic features diagnostic of sarcoidosis. In addition, atypical forms of sarcoidosis exist, and in such cases, the diagnosis may be challenging. Dr Rossi and colleagues summarize conventional and unusual histologic findings of sarcoidosis, with emphasis on the main differential diagnoses. In more than 90 % of cases, the disease manifests as intrathoracic lymph node enlargement, pulmonary involvement, skin or ocular manifestations or some combination of these findings. However, clinical manifestations are protean and non-specific. In addition, unusual patterns of organ involvement or granulomatous inflammation developing in uncommon locations for sarcoidosis can confuse further the clinical picture. This is discussed by Dr. Judson. Lung involvement may manifest with a wide spectrum of radiological appearances. In typical cases, chest radiography is usually sufficient to establish the diagnosis with little margin of error, whereas CT plays a critical role in several settings, including atypical clinical and/or radiographic findings and disease complications. Dr. Silva and colleagues summarize the more difficult imaging aspects of sarcoidosis. The management of sarcoidosis includes several crucial decisions the most important being whether the patient needs treatment. In addition, clinicians are often reluctant to start therapy due to both side effects of corticosteroids—the first-line therapy—and the difficulty in getting patients off therapy. Second-line agents include methotrexate and hydroxychloroquine—but these drugs are not always effective—whereas monoclonal antibodies to tumour necrosis factor and thalidomide may be helpful in patients with refractory disease. Drs. Baughman and Lower review key issues in the management of sarcoidosis.

This special issue of *Clinical Reviews in Allergy and Immunology*, with a multidisciplinary authorship of the highest standard, sets out to provide the most up-to-date thinking on all aspects of sarcoidosis. We hope it will contribute to stimulate those trying to fill the many gaps in our understanding of the disease and at the same time to guide clinicians caring for these challenging patients.

Compliance with Ethical Standards

Conflicts of Interest Paolo Spagnolo serves as consultant for Roche and has received consulting fees from Boehringer Ingelheim.

Informed Consent As there is no person or personal data appearing in the paper, there is no one from whom a permission should be obtained in order to publish personal data.

Research Involving Human Participants and/or Animals This article does not contain any studies with human or animal subjects performed by the authors.

References

1. Sharma OP (2005) Definition and history of sarcoidosis. Eur Respir Mon 32:1–12
2. Hutchinson J (1898) Mortimer's malady. A form of lupus pernio. Arch Surg (London) 9:307–315
3. Besnier E (1889) Lupus Pernio de la Face. Ann Derm Syph (Paris) 10:33–36
4. Boeck C (1899) Multiple benign sarcoid of the skin. Norsk Mag Laegevid 14:1321–1345
5. Heerfordt CF (1909) Uber eine febris uveo-parotidea subchronica. Graefes Arch Ophthalmol 70:254–258
6. Schaumann J (1933) Etude anatomo pathologique et histologique sur les localisations viscerales de la lymphogranulomatose benigne. Bull Soc Fr Dermatol Syphiligr 1:167–322
7. Lofgren S (1953) Primary pulmonary sarcoidosis. Acta Med Scand 145:424–455
8. Kveim A (1941) On a new and specific cutaneous reaction in Boeck's sarcoid: a preliminary report. Nord Med 9:169–172

9. Siltzbach LE (1961) The Kveim test in sarcoidosis: a study of 750 patients. J Am Med Ass 178:476–482
10. Zissel G (2014) Cellular activation in the immune response of sarcoidosis. Semin Respir Crit Care Med 35:307–315
11. Noor A, Knox KS (2007) Immunopathogenesis of sarcoidosis. Clin Dermatol 25:250–258
12. Spagnolo P, Grunewald J (2013) Recent advances in the genetics of sarcoidosis. J Med Genet 50:290–297
13. Newman LS, Rose CS, Maier LA (1997) Sarcoidosis. N Engl J Med 336:1224–1234
14. Spagnolo P, Richeldi L, du Bois RM (2008) Environmental triggers and susceptibility factors in idiopathic granulomatous diseases. Semin Respir Crit Care Med 29:610–619
15. Statement on Sarcoidosis. Joint statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. (1999). Am J Respir Crit Care Med. 160, 736-755
16. Rybicki BA, Major M, Popovich J Jr, Maliarik MJ, Iannuzzi MC (1997) Racial differences in sarcoidosis incidence: a 5-year study in a health maintenance organization. Am J Epidemiol 145:234–241
17. Grunewald J, Eklund A (2009) Löfgren's syndrome. Human Leukocyte Antigen strongly influences the disease course. Am J Respir Crit Care Med 179:307–312
18. Spagnolo P, du Bois RM (2007) Genetics of sarcoidosis. Clin Dermatol 25:242–249
19. Newman LS (2005) Aetiologies of sarcoidosis. Eur Respir Mon 32: 23–48
20. Judson MA (2003) The etiologic agent of sarcoidosis. What if there isn't one? Chest 124:6–8