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A Systematic Review of the Literature on Sarcoidosis: Early Recognition and Diagnosis

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Background

Sarcoidosis is a multisystemic granulomatous disorder, characterized by noncaseating granulomas affecting multiple body organs with the lungs (90%) most commonly involved [1]. Historically, sarcoidosis was first identified in 1877 by Dr. Jonathon Hutchinson and later characterized in 1899 by Dr. Caesar Boeck in an effort to describe skin nodules with the appearance of sarcoma hence the term "sarc" was derived [2]. According to Iannuzzi et al. sarcoidosis affects persons of all racial and ethnic backgrounds with a peak incidence at 20 to 40 years. Data from the National Center for Health Statistics notes greater than 23,000 deaths in the US from 1988 to 2007, with age-adjusted sarcoidosis mortality greater than 50% in women and 30.1% in men [3]. Swigris et al. [3] further notes the incidence of sarcoidosis in blacks is more than triple that of whites (35.5 cases versus 10.9 cases per 100,000) with greater prevalence among African American females. The overall average incidence in the US is 10-50/100,000 population [4].

A vast number of health determinants have been associated with developing sarcoidosis, such as: environmental exposure, tobacco use, race, and socioeconomic status [5]. Clinical presentation is highly variable with a diversity of symptoms frequently resulting in a delayed diagnosis [4,6]. The consequence of delayed diagnosis is advanced organ involvement with the lungs affected in greater than 90% of cases. Resultantly, the need for prompt diagnosis is vital in improving patient outcomes.

Review of the Literature

Methodology

A systematic review of the literature was executed to assess factors relative to recognition and diagnosis of sarcoidosis. The electronic databases incorporated in the search were: PubMed, EBM, MEDLINE, CINAHL, Cochrane, and hand searches. Relevant MeSH terms utilized in the search, included; sarcoidosis, early diagnosis of sarcoidosis, signs and symptoms in sarcoidosis, diagnostic testing in sarcoidosis, sarcoid, and pulmonary sarcoidosis. Inclusion criteria were as follows: 1) any research related to diagnostic testing in sarcoidosis, such as; radiologic, laboratory data, and tissue biopsy, 2) studies related to etiology and risk factors, 3) adult population only, and 4) any race or gender. Exclusion criteria were minimal, excluding literature relative to treatment of sarcoidosis. Studies were evaluated for level of evidence and relevance and categorized according the type of study, including: retrospective, case-control etiologic, descriptive, prospective observational, case studies, review of the literature, expert reviews, randomized control trial, and cohort. The refined search resulted in 57 articles specific to the topic of interest. Thirty-six articles were included in the literature review.

Synthesis of Data

Upon clinical presentation sarcoidosis symptoms are quite variable and often mimic symptoms of other disorders making the diagnosis elusive and challenging [4,7]. Judson, Thompson, Rabin et al. reported an average of three physician visits from the onset of symptoms to the time of diagnosis [8]. Variables associated with this study, included the number of physician visits (>6 months versus <6 months), initial onset and severity of pulmonary symptoms measured by chest radiography Scadding Stages, pulmonary function tests (PFTs), socioeconomic category (SES), and referrals to specialists. Findings from this study substantiated claims of delayed diagnosis of sarcoidosis with only 15.3% of participants diagnosed on initial visit. More physician visits were associated with patients exhibiting pulmonary symptoms (4.84 ± 0.38) versus those without pulmonary symptoms (3.15 ± 0.24), p=0.0002. Pulmonary function (FEV) was worse among patients diagnosed after six months compared to those diagnosed on the first visit. Higher Scadding Stages (II-IV) were associated with delayed diagnosis, however; race, SES and type of physician had no significant effect on time to diagnosis. Baughman et al. [13], Culver, and Judson concur with findings by Judson et al. [6] indicating several physician visits prior to diagnosis of sarcoidosis [4,8].

A recent review of radiologic manifestations of pulmonary sarcoidosis by Al-Jahdali and Rajiah et al. [9] propose that sarcoidosis is indeed a common disease with well-defined, identifiable features, yet, most physicians remain unfamiliar with atypical and often-unclear manifestations of thoracic sarcoidosis [9]. Furthermore, Al-Jahdali et al. [9] reports the association of increased morbidity and mortality with delayed identification of pulmonary involvement and therefore, implies the importance in correlating atypical imaging, clinical manifestations, and histologic findings. Sharma et al. discussed the benefit of CT scans versus chest radiographic (CXR) Scadding Scores in diagnostic staging of sarcoidosis (Table 1) [10]. Sharma et al. found that of 160 patients, 49 (31%) patients had stage I disease, 71 (44.3%) had Stage II, and 43 (26.8%) had Stage III disease. Whereas, the CT scan was superior in identifying interstitial opacities in 55% of patients with Stage I disease. The results of this study found that CT scans and CXRs are similar in Stages II and III, however, the CT scan more clearly defined abnormal lung findings in early stage (I) disease. Lynch discusses the usefulness of CT scans in sarcoidosis in a review article [11]. Given the variability of manifestation of pulmonary sarcoidosis, Lynch postulates that abnormal CXRs are common in 90-95% of patients diagnosed with sarcoidosis with findings of bilateral hilar lymphadenopathy (BHL) present in fifty to eighty percent. Findings in this review indicate the usefulness of CT scans to more clearly

delineate mediastinal and hilar granulomas; however routine CT scans are not applicable in initial diagnosis or management of sarcoidosis. In a retrospective analysis of fifty-six patients with pulmonary involvement of sarcoidosis, findings suggest high-resolution CT scans are useful in defining pattern and extent of disease [12]. Yeager et al. assessed the correlation between demographics and psychosocial influences with the level of respiratory function [13]. All patients in the study had biopsy positive lung involvement, measured by Scadding Stage, forced vital capacity (FVC) and dyspnea. Other variables incorporated, included demographic and psychosocial factors, which were measured using the Center for Epidemiologic Studies Depression Scale (CES-D) with scores ranging from zero to sixty. Yeager observed statistical significance in a reduced FVC when correlated with higher Scadding Stages ($p<0.0001$) [13]. Increased dyspnea was also found with higher Scadding stages (II-IV), while patients with higher depression scores (CES-D) were also associated with decreased FVC and dyspnea. Yeager also perceived an association between decreased lung function and radiographic staging (Scadding Stages). However, upon review of recent developments in assessment of sarcoidosis, Baydur postulates no distinct relationship between change in lung volumes and radiographic stage of disease [14]. Conclusions drawn from this study suggest a more comprehensive approach to diagnosing sarcoidosis, with consideration of psychosocial factors.

Stage 0	No lymphadenopathy or pulmonary infiltrates present
Stage I	Hilar and mediastinal adenopathy alone
Stage II	Adenopathy and pulmonary infiltrates
Stage III	Pulmonary infiltrates alone
Stage IV	Pulmonary fibrosis

Table 1: Scadding Staging System for pulmonary sarcoidosis (Scadding, 196, modified)

Demographic data was extracted from the ACCESS study where participants were recorded as either African American or Caucasian. African Americans were found to possess a higher incidence of disease [5]. Pulmonary sarcoidosis is discovered in greater than 90% of patients diagnosed with sarcoidosis according to Morgenthau & Iannuzzi [4,15]. Given the prevalence of pulmonary involvement, radiologic imaging plays a vital role in confirming and staging sarcoidosis. A descriptive study by Koyama et al. [16] suggests a more comprehensive approach in diagnosis of sarcoidosis by correlating clinical symptoms with radiologic findings since diagnosis is generally based on clinicoradiologic and pathologic findings. Even in the absence of clinical symptoms, diagnosis may be based on radiologic evidence of nodules within vital organs that may arouse suspicion. Findings in the study by Koyama et al. revealed cervical lymphadenopathy in one-third of patients enrolled, while dyspnea, cough and hilar adenopathy confirmed thoracic involvement. Koyama et al. observed cardiac involvement in 25% of patients, as well as, central nervous system (CNS) involvement in twenty-five percent [16]. In both cases, use of CT scan and magnetic resonance imaging (MRI) are useful in detecting abnormalities suggestive of sarcoidosis. Further use of radiologic evaluation is required in ocular involvement, occuring in approximately 20-50% of sarcoidosis patients. Takada et al. reported an incidence of ocular sarcoidosis in approximately 11-83% during the course of disease; nonetheless, the incidence at presentation (pre-diagnosis) is approximately1.5-12.4 percent [17].

Diagnosis of sarcoidosis is often confirmed by invasive tissue biopsy. In a randomized control trial performed in a university medical center, fifty patients with suspected sarcoidosis were enrolled. A comparison was made between outcomes of endobronchial ultrasound guided (EBUS)-guided transbronchial needle aspiration (TBNA) and standard TBNA. Tremblay et al. [18] found that outcomes were more favorable in the EBUS-guided TBNA group (83.3%) versus 58.3% in the standard TBNA group, an increase yield of 29.5% for the EBUS-guided TBNA group ($p<0.05$; 95% CI, 8.6 to 55.4). A prospective study of 62 patients conducted by Oki et al. (2012) [19] also found EBUS-guided TBNA to have a greater diagnostic yield and less invasive than transbronchial lung biopsy (TBLB) with a final diagnosis of sarcoidosis in 54 of the 62 patients enrolled.18 Conclusions from both studies (Oki and Tremblay) found the EBUS-guided TBNA superior to standard transbronchial biopsy methods. In a randomized clinical trial to comparing endosonographic mediastinal lymph node biopsy with conventional bronchoscopy (TBLB), von Bartheld et al., surmised overall superior diagnostic detection of granulomas with endosonography (80%) compared to 53% with conventional bronchoscopy [20]. The evidence strongly supports the use of EBUS-TBNA as the superior method of bronchial tissue biopsy in suspected or confirmed cases of sarcoidosis.

Sarcoidosis remains a disease of exclusion. While it generally occurs in 20-40 years of age, it is important to note that it may also occur in older patients over the age of fifty years. Lenner et al. [21] reviewed the medical records of 181 patients to evaluate characteristics between two groups: Group A consisting of those over age 50 years (92), and Group B (89) consisting of those diagnosed prior to age fifty years. Similarities in race, gender, tobacco use, presenting symptoms, organ involvement, PFTs, radiographic stage of disease, PPD status and lab values were found. Lenner et al. noted decreased diffusion capacity as the most prevalent PFT abnormality in both groups presenting with respiratory symptoms. The majority of patients between groups had progressive disease based on Scadding Staging (Appendix). The lungs, lymph nodes and skin were noted as the most common organ system involved. Conclusions drawn from this review suggests no significant difference in clinical manifestations of sarcoidosis regardless of age, therefore; diagnosis of sarcoidosis should be considered in any patient presenting with characteristics signs and symptoms. Social predictors have been evaluated in several studies resulting from data obtained in the original ACCESS (A Case Control Etiologic Study of Sarcoidosis).

Clinical evidence regarding various aspects of disease is often found in literature reviews. Belfer & Stevens in a primary care review noted 3 criteria for diagnosis of sarcoidosis [22]. These criteria include: (1) presence of clinical and radiographic findings which are consistent with sarcoidosis, (2) confirmation of noncaseating granulomas by tissue biopsy from one or multiple sites, and (3) exclusion of differential diagnosis of granulomas, measured by appropriate histochemical, serologic and microbiologic testing. Additionally, Spagnolo et al. [23] suggest a thorough history and physical are also essential to diagnosis [23]. In 2004, Wu and Rashcovsky provided an expert review of possible etiology of sarcoidosis, presenting clinical symptoms, diagnosis and treatments [24]. Conclusions drawn by Wu and Rashcovsky suggest etiology may be environmentally driven and genetically predestined. This review further suggest, infection should always be ruled out with the presence of lymphadenopathy and a chest x-ray with any pulmonary symptoms. Rabin et al. concluded from a case-control etiologic study of 696 subjects (recruited from ACCESS), that low socioeconomic status (SES), lack of insurance, race, gender, and age are associated with severity of disease on clinical presentation

[25]. Severity of disease was defined as dyspnea or shortness on presentation. Coefficients from the logistical regression model were analyzed using dependent variables, using odds ratio with 95% CI. Findings further suggest the existence of a relationship between late presentation and severity of pulmonary disease.

Iannuzzi et al. [2] found associations between sarcoidosis and moldy environments, chemical exposure to pesticides and insecticides [2]. The focus of the review by Iannuzzi et al. [2] included identification of sarcoidosis symptoms, including; fatigue, night sweats, fever and unexplained weight loss. Iannuzzi et al., notes the need for comprehensive biochemical testing as indicated. Newman and Newman summarized findings from recent investigations that provide evidence for both occupational and environmental causes of granulomatous inflammation observed in sarcoidosis [26]. Talmadge discusses current clinical manifestations and diagnosis of sarcoidosis in a review of the literature [27]. Talmadge's findings are consistent with previously discussed clinical manifestations, including: pulmonary (90%) and extrapulmonary involvement, fatigue, malaise, fever, and weight loss. Recommended diagnostic test, include; chest radiograph, CT and PET scans where indicated, laboratory tests, and histopathologic detection of noncaeseating granulomas. In cases of patients presenting with Lofgren's syndrome (erythema nodosum, fever, arthritis, and lymphadenopathy), diagnosis is likely certain. Talmadge cites the current prevalence of sarcoidosis as 10-40/100,000.

Sarcoidosis etiology was reviewed by Morenthau and Iannuzzi [15] from a prospective multi-center case-control etiologic study of 700 subjects with newly diagnosed sarcoidosis and matched control subjects [14]. Findings from this study suggest identification of possible genes, as well as, Mycobacterium tuberculosis catalase-peroxidase protein (p. 174), which may be associated with sarcoidosis. Specific chromosomes (6p22.3 and 8p12) have been identified in African Americans with sarcodiosis. While the diagnosis of sarcoidosis remains indeterminate, researchers are studying the genetic aspects of this disease with promising forecasts for the future. The possibility of genetic etiology has also been explored by Baughman et al. in an expert review [4]. The focus of the review was an update on sarcoidosis etiology, diagnosis and treatment. Although sarcoidosis is viewed as an old disease, the etiology remains in question. Baughman et al. contends delayed diagnosis in sarcoidosis remains common. While strides have been made in the area of genetic predisposition as measured by Genome-Wide scans, immunopathogenesis of sarcoidosis remains vague. The BTNL2 gene has also been isolated, prompting further research. Mehrotra and Dhingra propose the effectiveness of cytological evaluation of granulomas in suspected sarcoidosis [28]. More efficient diagnostic technology, such as EBUS and positive emission tomography (PET) scans, has been incorporated in diagnosis of sarcoidosis. Cozier, Berman, Palmer et al. evaluated data from the Black Women's Health Study (ACCESS), a cohort of 59,000 black females throughout the US [5]. The purpose of the prospective study was to review epidemiologic data on incidence, prevalence, and clinical characteristics of sarcoidosis. Data was obtained through surveys obtained twice a year. The study results reveal, "685 prevalent cases at baseline in 1995 and 435 incident cases" reported over 12 years of follow up (p. 147). Cozier et al. approximated a yearly incidence rate of sarcoidosis of 71/100,000 and existing prevalence of two-percent [5]. The median prevalent age of diagnosis was 32 years. High variability was noted on clinical presentation. In the ACCESS trial, 95% of participants had lung involvement, followed by lower percentages of skin lesions (erythema nodosum), lymph node, eyes, liver and joint involvement. Comorbidities are also thought

to contribute to the incidence of sarcoidosis. This study offers confirmation of preceding reports of high incidence and prevalence of sarcoidosis among black female.

Sarcoidosis may present clinically as cutaneous skin lesions. In appraisal of cutaneous manifestations of sarcoidosis, Pruystowsky and Sanchez examined types and appearance of cutaneous sarcoid lesion [29]. The lesions may present in various forms, such as; nodules, papules, plaques, and infiltration of scars, characterized by histopathologic features in approximately 25% of patients diagnosed with sarcoidosis. Pathogenesis remains unclear, however, thought to be genetically associated. Further studies are warranted on cutaneous sarcoidosis.

Case studies are useful in providing evidence-based data to researchers. Spagnolo et al. [22] summarized the findings of a case study [22]. A 58 year-old male with a TBNA confirmed sarcoidosis was treated with steroids on initial diagnosis. Several years later, the patient presented with a 3-month history of fever, fatigue, weight loss, and abdominal pain. Workup for recurrent disease revealed thrombocytopenia, hepatosplenomegaly, and a left pleural effusion. Cultures obtained from pleural fluid were positive for Mycobacterium tuberculosis. The infection was treated and the patient recovered. In conclusion, a differential diagnosis should always be considered since sarcoidosis may have an atypical presentation. Clinicoradiologic and pathologic evaluation is crucial in the sarcoidosis population [10]. Chadha et al. [30] discussed a case report involving a 36 year-old male pilot who presented with a two year history of recurrent nodules and plaques on his back, shoulder and face [30]. He was initially misdiagnosed and treated for cutaneous tuberculosis. Four years from initial onset of skin lesions, a second misdiagnosis of leprosy was made. Finally, the patient was diagnosed with sarcoidosis based on CXR and CT findings of pulmonary hilar adenopathy. Further laboratory (lab) data revealed an elevated angiotensin converting enzyme (ACE), abnormal PFTs and elevated serum calcium level. No evidence of multisystemic involvement. Treatment was initiated with complete resolution of lesions. Recommendations from this case report suggest the necessity of a tissue biopsy to evaluate for specific histiologic characteristics of noncaseating granulomas. As evidenced by this case report, sarcoidosis diagnosis is often delayed or misdiagnosed. A case presentation by Iannuzzi and Fontana involves a black female in her sixties who presented with an 8-year history of a chronic nonproductive cough, dyspnea, lymphadenopathy and fatigue with a suspicion for sarcoidosis [30]. Subsequent PFTs showed moderate restriction of lung capacity and significant impairment in diffusion, with marked interstitial infiltrate on CT scan. The patient was treated with high dose steroids and eventually recovered some degree of lung function. Delayed diagnosis of sarcoidosis results in significant pulmonary debilitation and increased mortality [31].

Summary

A systematic review of the literature significantly documents early symptoms of sarcoidosis and recommendations for diagnostic evaluation. Within the review process articles were evaluated for etiology, risk factors, diagnostic testing, and criteria for diagnosis. Several of the studies attained similar conclusions. Etiologic data, incidence and prevalence were consistent throughout the review. Inconsistency was noted regarding SES as a predictor for severity of disease. The literature also consistently differentiates the appropriate indication for various radiologic testing mechanisms. Overall, the systematic review was informative. Limited studies in sarcoidosis

presented a challenge in the review process. The majority of the published studies were secondary studies based on the ACCESS study conducted from 1995-2005, creating a gap in published literature. Over the past eight years significant research publications have emerged, specifically relating to genetics, pulmonary, and extra-pulmonary manifestations of sarcoidosis, including: ocular, cardiac, and neuro-sarcoidosis. The evidence supports necessity for early diagnosis of such a debilitating disease to improve patient outcomes.

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