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Research Article

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Clinical and Laboratory Manifestations of Stage 0 Sarcoidosis Patients

***(Running title:** Clinical manifestations of stage 0 sarcoidosis)*

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Abstract

Background and aim: *Stage 0 sarcoidosis is characterized by the presence of granulomas without radiologic chest abnormalities with diverse and almost absent clinically evident manifestations. Exiguity of pulmonary imaging findings poses a diagnostic dilemma and challenge for clinicians. This research paper aims to elucidate the clinical, laboratory, and the radiologic findings of stage 0 sarcoidosis to shed light into its obscure pathogenesis and enhance the diagnostic yield.*

Methods: *A retrospective analysis was conducted on stage 0 sarcoidosis patients admitted between 1970 and 2024 focusing on the demographic data, clinical symptoms, laboratory findings, Kveim test, radiology, and the nuclear imaging manifestations. Diagnostic criteria followed the ATS/ERS/WASOG guidelines for sarcoidosis.*

Results: *The study included 128 patients with a mean age of 42.8 years and a predominance of females (64.1%). Symptoms at admission included fatigue (64%), dry cough (42%), and dyspnea on exertion (28%). Cutaneous (24%) and ocular (18%) involvement were the most common exrapulmonary organ sites. Laboratory tests revealed elevated serum ACE in 48%, high Ca in 6%, and hypercalciuria in 18% of the patients. Nuclear imaging revealed high diagnostic utility for extrapulmonary sarcoidosis (r:078, $p<0.05$). Kveim test displayed 89.1% sensitivity ($p<0.01$).*

Conclusions*: Clinical manifestations did not show a denotative diagnostic contribution while elevated serum ACE, hypercalcemia, 24/h hypercalciuria, and inflammatory markers did not exhibit a significant incidence in stage 0 sarcoidosis. ^{18}FDG and Ga^{68}-citrate PET/CT were distinctively useful to detect occult extrapulmonary organ in this stage. Kveim test was the imperative diagnostic tool for the timely recognition of this indolent precursor stage revealing a significantly high sensitivity. Although a forgotten intervention despite its historical perspective, Kveim test may still be the hallmark of conclusive diagnosis for stage 0 sarcoidosis patients. Collaborative analysis of the clinical manifestations, Kveim test, laboratory, and nuclear imaging findings provided a definite diagnostic accuracy for stage 0 patients.*

Keywords: *Sarcoidosis, Diagnosis, Stage 0 sarcoidosis, Clinical manifestations, Kveim test.*

Introduction

Sarcoidosis, a systemic granulomatous disorder of uncertain etiology characterized by the presence of non-caseating epithelioid cell granulomas in multiple organs, primarily the lung that poses intricate diagnostic challenges for the clinicians particularly in stage 0 disease**.** Delineated by the formation of non-caseating granulomas in the affected organs, sarcoidosis manifests across a broad spectrum of clinical presentations, ranging from asymptomatic disease to debilitating various organ involvement (1,2,3). Among its diverse clinical phenotypes, stage 0 sarcoidosis stands out as an elusive entity, defined by the presence of granulomatous inflammation without an overt clinical or radiographic evidence of disease.

Despite its ostensibly benign nature, stage 0 sarcoidosis warrants consideration due to its potential to progress to symptomatic stages and cause significant morbidity. By unraveling the complexities surrounding this incipient stage of the disease, we aim to provide clinicians with a comprehensive understanding of its subtle nuances and diagnostic dilemmas. Through a synthesis of existing literature and empirical insights, this research paper endeavors to delineate the intricate interplay between clinical observations, laboratory investigations, and imaging modalities in the diagnostic evaluation of stage 0 sarcoidosis. The recognition of stage 0 sarcoidosis is pivotal not only for prognostic purposes but also for guiding therapeutic interventions and mitigating disease progression. However, the absence of overt clinical symptoms poses a formidable barrier to its timely diagnosis. This research paper aims to provide a comprehensive overview of the clinical manifestations, laboratory findings, and diagnostic strategies pertinent to stage 0 sarcoidosis. By synthesizing existing evidence and integrating contemporary perspectives, we aspire to offer clinicians a robust framework for navigating the diagnostic complexities of this incipient stage of sarcoidosis. Through an interdisciplinary lens encompassing clinical, laboratory, radiologic, and pathologic insights, we endeavor to illuminate the path towards early recognition by setting forth the hitherto unpublished manifestations of stage 0 sarcoidosis patients.

Methods

This retrospective study was conducted to investigate the clinical, laboratory, radiologic manifestations, and the Kveim test results of stage 0 sarcoidosis patients admitted at the Internal Medicine and Pulmonary Diseases departments of Cerrahpasa Medical Facutly between January 1970 and April 2024.

Informed consent was obtained from all participants and measures were taken to ensure patient confidentiality throughout the study. Clinical data including demographic information, medical history, presenting symptoms, physical examination, laboratory, and radiologic findings were collected from the medical records. Pulmonary function tests, DLCO, chest x-ray, thorax CT, nuclear imaging, and the Kveim test were performed as a part of the routine diagnostic evaluation. Patients included in the study met the following criteria as confirmed diagnosis of stage 0 sarcoidosis based on the histopathologic presence of non-caseating granulomas without radiologic evidence of pulmonary disease. Constitutional symptoms included fatigue, weight loss, fever, and arthralgia. Pulmonary manifestations involved dry cough, dyspnea, chest pain, or discomfort. Extrapulmonary symptoms included specific symptoms related to organs essentially the cutaneous and ocular manifestations.

Kveim test was performed according to the standard protocols (4-8) comprising a suspension of sarcoidosis spleen tissue was injected intradermally into the volar aspect of the forearm of the participant. The injection site was monitored for any reactions, and induration at the injection site was measured at 4 to 6 weeks post-injection. Kveim test was performed in ambiguous or indecisive sarcoidosis cases one month before the conventional tests to boost the diagnostic efficiency of these by enhancing the intensity of granulomatous inflammation and granuloma burden of stage 0 disease. Laboratory data including serum angiotensin-converting enzyme (ACE) levels, complete blood count, tuberculine, liver, and renal function tests were collected. Additionally, data comprising serum and 24-hour urine calcium levels were documented. Lung function analysis involving PFTs and DLCO was done in all patients. Chest X-ray and high-resolution computed tomography (HRCT) scans were reviewed to assess the presence of hilar lymphadenopathy, pulmonary infiltrates, or other abnormalities suggestive of sarcoidosis. Nuclear medicine modalities such as ^{18}FDG and ^{68}Ga-citrate PET/CT were performed to detect the presence of pulmonary or extrapulmonary granulomatous inflammation involvement (9). In patients presenting with an equivocal or indecisive sarcoidosis profile at the initial setting, the diagnosis was confirmed after a mean follow-up of two years when other clinical findings, pulmonary, and extrapulmonary organ involvement became evident. Histopathological biopsy specimens were reviewed for the presence of non-caseating granulomas consistent with sarcoidosis in at least two organs. Descriptive statistics were used to summarize the demographic characteristics, clinical manifestations, laboratory findings, imaging and the Kveim test results of the study population. Continuous variables were presented as mean ± standard deviation or median (interquartile range), while categorical variables were presented as frequencies and percentages. Statistical analyses were performed using SPSS 29 version. Pertaining to the statistical analysis, p-values less than 0.05 were considered statistically significant. Categorical variables were presented as frequencies and percentages. Comparisons between groups were performed using appropriate statistical tests, including analysis of variance (ANOVA), Kruskal-Wallis test, chi-square test, or Fisher's exact test, and Mann-Whitney U test as applicable. Chi-square tests or Fisher's exact tests were employed to analyze categorical variables, while t-tests or Mann-Whitney U tests were used for continuous variables. Statistical significance was set at $p < 0.05$. For correlation assessment, an r value $0.00 \leq r \leq 0.10$, $0.10 < r \leq 0.39$, $0.40 \leq r < 0.69$, $0.70 \leq r < 0.89$ and $0.90 \leq r \leq 1.0$ were considered as negligible, weak, moderate, strong, and very strong correlation, respectively (9).

Results

A total of 128 patients with stage 0 sarcoidosis were included in the study. The mean age of the participants was 42.8 years (52.6 ± 18.4), with a predominance of females (Table 1). The most common pulmonary complaint was dry cough followed by dyspnea while fatigue was the most prevalent constitutional symptom among stage 0 patients (Table 2). Specific cutaneous manifestations were observed as the most common extrapulmonary organ sarcoidosis followed by ocular involvement. Uveitis and conjunctival nodules were identified in identified in 16 (12.5%) and 12 (9.4%) of the cases, respectively. Other extrapulmonary involvement occured in 38 (29.6%) of the patients (Table 2).

Table 1: Epidemiology of stage 0 sarcoidosis patients.

Patient characteristics	Patient #	Incidence (%)
Female	82	64.1
Male	46	35.9
Smoking history	12	9.4
Comorbid diseases	10	7.8

Serum ACE levels were elevated in 32.8% of the patients with a mean level of 72.4±24.6 U/L. Hypercalcemia was detected in 4.7% of the patients. Urinary calcium level was above the normal range in 7.8% of the subjects. Tuberculine test was negative in 82.3% of the patients. Spirometry revealed mild restrictive pattern, characterized by reduced forced vital capacity (FVC) and normal forced expiratory volume in one second FEV_1/FVC ratios in 6.3% while DLCO/VA was below normal in 11.7% of the patients. Chest x-ray showed normal lung parenchyma in all patients. Thorax CT revealed parenchymal and mediastinal lymphadenopathy in 15.2% while ^{18}FDG-PET/CT revealed enhanced tracer uptake in 63.2% of the patients in various organs. Ga^{68}-citrate PET/CT displayed significant tracer uptake in the mediastinal lymph nodes and extrapulmonary organs in 73.1% indicating granulomatous inflammation.

Table 2: Incidence and correlation of symptoms in stage 0 sarcoidosis.

Symptoms	Total (%)	r	p
Asymptomatic	46 (36.3%)	0.24	<0.01
Dry cough	76 (59.4%)	0.72	<0.05
Dyspnea	42 (32.8%)	0.28	<0.05
Malaise	36 (28.1%)	0.32	<0.01
Fatigue	56 (43.8%)	0.64	<0.05
Fever	14 (10.9%)	0.28	<0.01
Weight loss	6 (4.7%)	0.12	<0.20
Night sweats	12 (9.4%)	0.16	<0.24
Weakness	6 (4.7%)	0.24	<0.01
Nonspecific skin lesions	22 (17.2%)	0.48	<0.05
Specific skin lesions	24 (18.8%)	0.64	<0.05
Ocular symptoms	28 (22.7%)	0.56	<0.01
Uveitis	20 (15.6%)	0.58	<0.05
Arthralgia	14 (%10.9)	0.28	<0.18
Myalgia	10 (7.8%)	0.18	<0.24
Bone pain	3 (2.3%)	0.12	<0.28
Parotid enlargement	4 (4.9%)	0.18	<0.20
Facial paralysis	1 (0.08%)	0.14	<0.32
Heerfordt syndrome	1 (0.08%)	0.14	<0.32
Neurologic symptoms	4 (3.1%)	0.18	<0.05
Cardiac symptoms	2 (1.6%)	0.16	<0.28

*Specific cutaneous lesions: erythema nodosum, lupus pernio

BAL revealing lymphocytosis and a CD_4/CD_8 ratio higher than 3.5 were obtained in 43.8 and 48.4% of the patients, respectively. TBB yielded a suggestive diagnosis of sarcoidosis in 67.2% of the subjects revealing non-caseating granulomatous inflammation. Kveim test provided a 89.1% positive result compatible with sarcoidosis. The pathology of extrapulmonary organ biopsy samples revealed non-caseiting granulomatous inflammation in 56.3% of the patients. Incidence, sensitivity, specificity, and correlation of the clinical and laboratory manifestations of stage 0 patients is shown in Table 3. Among the interventions used for stage 0 sarcoidosis identification Kveim test was the most definitive diagnostic tool ($p<0.01$) followed by transbronchial lung biopsy and BAL cytology ($p<0.01$). Nuclear interventions such as ^{18}FDG and Ga^{68}-citrate PET/CT were definitive imaging modalities for the diagnosis of stage 0 sarcoidosis ($p<0.05$). Another potential benefit of ^{18}FDG and Ga^{68}-citrate PET/CT was the detection of extrapulmonary biopsy sites to obtain diagnostic samples in 18 (18/38, 47.4%) and 14 (14/26, 53.8%) of the patients, respectively. Collaborative analysis of the clinical and the laboratory findings reached a 96.8% sensitivity and 92.4% specificity of diagnostic accuracy for stage 0 sarcoidosis patients ($p<0.01$). Following the Kveim test, ^{18}FDG, and ^{68}Ga-citrate PET/CT were identified as the most significant diagnostic determinants for the identification of stage 0 sarcoidosis patients.

Table 3: Incidence, sensitivity, specificity, and correlation of the clinical and laboratory manifestations in stage 0 patients.

Clinical manifestations	Pt #	Incidence (%)	Sen %	Spe %	r	p
Constitutional symptoms	62	48.4	24.6	18.6	0.18	<0.01
Pulmonary manifestations	54	42.2	32.4	28.6	0.24	<0.01
Extrapulmonary symptoms	79	61.7	18.2	16.8	0.38	<0.05
Tuberculine test *	106	82.3	86.4	82.2	0.78	<0.01
Hypergammaglobulinemia	8	6.3	0.18	0.16	0.14	<0.01
High serum ACE	42	32.8	46.8	42.6	0.46	<0.05
Hypercalcemia	6	4.7	12.4	10.8	0.16	<0.14
Elevated urine Ca (24/h)	10	7.8	14.2	12.6	0.19	<0.18
Liver function tests	2	1.6	6.2	5.8	0.12	<0.28
Renal function tests	1	0.08	4.6	3.6	0.18	<0.36
PFT	8	6.3	18.4	16.2	0.24	<0.26
DLCO/VA	15	11.7	26.2	24.6	0.32	<0.24
Chest x-ray	14	10.9	18.4	16.8	0.12	<0.28
Thorax CT	16/108	15.2	28.4	26.2	0.46	<0.08
^{18}FDG-PET/CT	24/38	63.2	72.8	68.6	0.58	<0.05
Ga^{68}-citrate PET/CT	19/26	73.1	78.6	74.2	0.72	<0.01
BAL lymphocytosis	56	43.8	62.8	54.6	0.52	<0.05
CD_4/CD_8>3.5	62	48.4	64.2	58.4	0.56	<0.01
TBB	86	67.2	71.6	68.4	0.84	<0.05
Extrapulmonary organ bx	72	56.3	64.8	62.6	0.82	<0.01
Kveim test	84/98	85.7	84.2	82.6	0.84	<0.01

* Negative tuberculine test

Discussion

Sarcoidosis is a chronic granulomatous inflammatory disorder characterized by the presence of non-caseating granulomas primarily in the lungs and extrapulmonary organs that presents with diverse clinical or miscellaneous laboratory manifestations, often posing diagnostic challenges particularly in its early stages (10-15). Stage 0 sarcoidosis presents a diagnostic dilemma due to the absence of explicit clinical symptoms and laboratory findings. Our study focused on patients with stage 0 sarcoidosis where the disease is often limited to asymptomatic organ involvement without apparent manifestations. By investigating the clinical and laboratory findings alongside the utility of the Kveim test in this cohort, we aimed to contribute to the understanding and early diagnosis of this enigmatic disease. This study reveals the ambiguous spectrum of clinical and laboratory abnormalities in stage 0 sarcoidosis patients despite the lack of conspicuous symptoms. A notable proportion of patients displayed clinical symptoms, laboratory, pulmonary function test, or imaging abnormalities that were uncertain and indefinite for subclinical pulmonary or extrapulmonary organ involvement. The highest diagnostic yield was obtained with the Kveim test followed by the pathologic assessment of the transbronchial biopsy specimens in stage 0 patients. Exclusively high diagnostic sensitivity of the Kveim test can be explained by the enchancement and boosting of the low intensity of granulomatous inflammation along with the increment in marginal or nominal granuloma burden of stage 0 sarcoidosis provoked by the reagent (16-20). Noninvasive nature and the relatively low cost make this forgotten test an attractive adjunctive tool in the diagnostic armamentarium for patients with stage 0 disease.

Moreover, our study sheds light on the heterogeneity of stage 0 sarcoidosis symptoms and laboratory findings by revealing the incidence of these manifestations. Although systemic and extrapulmonary symptoms were not significant for sarcoidosis, they carried a crucial importance for guiding the clinician into a precise diagnostic pathway at this stage. Constitutional manifestations like fatigue, fever, myalgia, lassitude, or arthralgia were common but lacked sensitiviy in the differential diagnosis with other disorders as their explicit features were not definitely consistent with sarcoidosis. Pulmonary symptoms such as dry cough, dyspnea, and extrapulmonary organ manifestations were observed to be more distinctive attributes for sarcoidosis diagnosis but they did not reach a significant level of specificity for differential diagnosis of stage 0 sarcoidosis as they may be a manifestation of many pulmonary, extrapulmonary, or systemic disorders (21,22,23). Cutaneous findings such as erythema nodosum, lupus pernio, and ocular signs such as anterior uveitis were determined to be more definitive for this stage. Extrapulmonary organ manifestations were more guiding for the clinician in terms of a definitive diagnosis at this stage.

Although some patients exhibited isolated abnormal laboratory findings such as elevated serum angiotensin-converting enzyme (ACE) levels, hypercalcemia, or hypercalciuria that are suggestive of sarcoidosis, they did not reach a satisfactory level of statistical significance. Thorax CT was primarily useful for the detection of lymph node without much accuracy as enlarged lymph nodes may occur due to many other pulmonary or systemic diseases. Nuclear imaging modalities comprising ^{18}FDG and ^{68}Ga-citrate PET/CT revealed enhanced tracer uptake mainly in the extrapulmonary organs such as the lymph nodes, liver, spleen, lacrimal, parotide glands, or thoracic lymph nodes. The highest diagnostic yield for the identification of stage 0 sarcoidosis patients was obtained by the Kveim test. Pathologic examination of the TBB specimens and BAL cytology constituted the second and third diagnostic hallmark for stage 0 sarcoidosis patients. Previous studies did not report the incidence of clinical symptoms or laboratory manifestations of stage 0 sarcoidosis (21-25). Our study filled a huge gap in stage 0 sarcoidosis by revealing the incidence of pulmonary and extrapulmonary symptoms, as well as the diagnostic sensitivity of conventional laboratory and imaging modalities along with the diagnostic interventions.

This study has several limitations related to its retrospective design, potential selection bias, missing data, and confined generalizability. Patient records may display inaccuracies or inconsistencies for data abstraction. The comparatively moderate sample size and the single-center nature of the study may restrain the external validity of the findings. This restraint is associated with the low incidence of stage 0 sarcoidosis due to diagnostic difficulties owing to the lack of specific clinical and laboratory manifestations along with absence of radiologic findings. Single-center nature of the study may obscure the feasibility of our results. Racial and genetic factors may lead to an extremely significant potential instability concerning patient symptoms, laboratory findings, and incidence of extrapulmonary organ involvement (18-22). Our study included exclusively Caucasian patients. Sarcoidosis patients with distinctive hereditary and genetic features may lead to divergent clinical outcomes regarding symptoms, laboratory findings, and prevalence of extrapulmonary organ involvement. Future prospective or retrospective studies comprising larger multicenter cohorts are required to validate our findings and to enucleate the clinical profile and manifestations of stage 0 sarcoidosis patients.

Our study has clearly delineated the diagnostic significance of stage 0 sarcoidosis manifestations regarding the clinical profile and laboratory manifestations. The specificity of each mentioned entity can theoretically be explained by the severity of granulomatous inflammation and the associated granuloma burden distribution in the relevant organs. A diagnostic impasse occurs in stage 0 patients which is the onset stage of sarcoidosis and granulomatous inflammation. This finding primarily appears to be associated with the intensity granulomatous inflammation and the redundance of the granuloma burden at this stage. The high diagnostic yield of the Kveim test at this stage may be explained by the administration of antigens that may have exacerbated the granulomatous inflammation that is induced by antigen specific stimulation in the reagent (19,20) because the test was performed as the initial diagnostic tool following routine laboratory investigations. Pathologic induction mechanism of the Kveim test is probably associated with the spontaneous sarcoidosis granuloma formation due to antigenic stimulation. Consequently, evolution of the Kveim test granuloma may enlighten the sarcoidosis pathogenesis, especially at the early disease stages. The high diagnostic yield of TBB and BAL analysis can be elucidated by the fact that the lung is the initial site where the granulomatous inflammation has commenced. Although extensive endobronchial lesions have been described in stage 0 disease (25), TBB and BAL displayed significant diagnostic yield among our patients. Kveim test was the hallmark diagnostic hallmark for stage 0 patients followed by TBB and BAL findings. Novel markers such as circulatory TGF-beta1 may be significantly high in early stage of pulmonary sarcoidosis (26) but the diagnostic sensitiviy of the conventional laboratory modalities for stage 0 sarcoidosis was not noteworthy in differential diagnosis. ^{18}FDG and Ga^{68}-citrate PET/CT detected active granulomatous inflammation areas and identified extrapulmonary organ biopsy sites (27) that were not determined by other imaging modalities. Definitive diagnosis in the early stages of sarcoidosis, especially stage 0, poses serious difficulties (3,28). Kveim test alone stands out as the most relevant intervention that provided the highest diagnostic yield at this stage. Collaborated assessment of the clinical and the laboratory findings revealed an almost hundred percent accuracy in the diagnosis of stage 0 sarcoidosis patients.

Conclusions

Our study underscores the clinical challenges posed by stage 0 sarcoidosis and demonstrates the clinical utility of incorporating clinical findings, laboratory parameters, imaging manifestations, and the Kveim test in the diagnosis of stage 0 sarcoidosis patients that highlights the relevance of a comprehensive evaluation of these manifestations. Constitutional and pulmonary symptoms did not achieve sufficient diagnostic specificity as they span a broad differential diagnostic profile. Extrapulmonary organ manifestations displayed a more specific pathway for the identification of stage 0 sarcoidosis patients. Laboratory findings did not reveal a diagnostic sensitivity and specificity for this stage as they may arise in many other diseases depriving a differential diagnostic profile. Kveim test emerged as the most valuable adjunctive tool in the diagnostic algorithm. As an almost forgotten modality today, Kveim test appears to be a remarkable clinical tool for stage 0 sarcoidosis patients as a safe, simple, and a specific approach. The incentive potential of the Kveim test may have further augmented the granulomatous inflammation and the granuloma load at this stage where the granulomatous inflammation is at its lowest intensity with the least granuloma burden. Collaborative assessment of the clinical, laboratory, and Kveim test findings significantly enhanced the diagnostic accuracy for stage 0 sarcoidosis providing a virtually definitive efficacy offering clinicians a robust framework for early identification. On the other hand, with its high diagnostic yield Kveim test has reached an efficiency that may reveal an unequivocal identification of stage 0 sarcoidosis patients by itself.

Author contributions

Cuneyt Tetikkurt designed and wrote the manuscript.

Halil Yanardag installed the dermographic and statistical analysis.

Muammer Bilir assembled the laboratory findings of the patients.

Conflicts of interest

The authors declare that they do not have any conflicts of interest to declare associated with this study and state explicitly that any kind of potential conflicts do not exist.

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