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Diagnostic yield of the Kveim test in sarcoidosis patients

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Abstract. *Background and aim:* Sarcoidosis is a granulomatous disorder of unknown etiology characterized by the existence of non-caseating granulomatous inflammation. Diagnosis can be challenging due to the presence of comprehensive clinical, laboratory, and radiologic manifestations. We have evaluated the diagnostic yield of the Kveim test and compared this test with the other conventional laboratory modalities. Our aim was to reach the highest level of diagnostic confidence acknowledging the absolute uncertainty in diagnosis with the current diagnostic enterprises. *Methods:* Medical records of 300 sarcoidosis patients were reviewed. Patients were classified into two categories as the conventional laboratory and the Kveim test group to compare the diagnostic yield. *Results:* Sensitivity of the Kveim test was 76.4% while the conventional laboratory tests provided a 64% diagnostic yield. The conventional tests had a low diagnostic rate in the early disease stages. Kveim test revealed a high yield diagnosis for all stages of sarcoidosis. Integrated assessment of the two modalities reached a 96.8% sensitivity and a 94,6% specificity. *Conclusions:* Conventional laboratory modalities were useful for the assessment of disease activity and identification of organ involvement. Kveim test revealed a significant diagnostic yield for all stages of sarcoidosis. The lowest output was achieved in stage IV patients due to the waning of active granulomatous inflammation. The highest diagnostic sensitivity was obtained by an integrated analysis of the conventional laboratory and the Kveim test results for all aspects of sarcoidosis.

Key words: Kveim test, sarcoidosis, diagnosis, laboratory tests

Introduction

Sarcoidosis is a multisystemic granulomatous disease with an unknown etiology and uncertain pathogenesis (1-4). Sarcoidosis poses a major challenge for diagnosis. This confrontation emerges as the presentation, clinical profile, laboratory, radiologic, and even the pathologic manifestations of sarcoidosis are shared by many other disorders including the lung or other organ systems thereby leading to a missed or overdiagnosis in many patients. Almost all the laboratory and imaging methods have remained far from providing an adequate precision for diagnosis until today. Disease stage, activity of granulomatous inflammation, and specificity of the laboratory findings emerge as the major contributing factors concerning the diagnosis or the clinical assessment of sarcoidosis. Primary objective of sarcoidosis diagnosis is the demonstration of non-caseating granulomas in 2 or more organs in a patient revealing a compatible clinical and radiological profile along with the exclusion of other diseases displaying similar histopathological features. Even the presence of granulomatous inflammation in two organs may remain insufficient without a compatible clinical Kveim test in sarcoidosis profile for some patients. Consequently, the highest level of confidence in sarcoidosis has been altered from a definite to a highly probable diagnosis as an absolute certainty in diagnosis may not achievable occasionally (5-6).

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Failure to meet the absolute certainty criteria for the identification of sarcoidosis can lead to a stringent diagnostic dilemma for clinicians. Sarcoidosis may imply a diagnosis of exclusion, require a clinical follow-up for two years, and entails an individual patient assessment. We have evaluated the diagnostic yield of the Kveim test in our patients to delineate the clinical utility of this procedure relevant to disease stage. The main target was to reach to an absolute certainty for the diagnosis of sarcoidosis patients. The second aim was to transact a comparative analysis of the Kveim test with the current laboratory and imaging modalities of sarcoidosis for the assessment of an accurate final diagnosis.

Methods

A total of 300 sarcoidosis patients admitted between 1964 and 1996 participated in the study comprising 174 (58%) females. Ethical Committee of Cerrahpasa Medical Faculty authorized (Ethical Committee registration number of is E-83045809-903.99-775196) and approved the study. The mean age of the patiens was 38.2±16.4 years. Conventional laboratory and Kveim test were done in all subjects. The patients were classified as the conventional test and the Kveim test groups. Conventional laboratory data included complete blood count, serum biochemistry, ERS, gammaglobulines, serum ACE, Ca, 24/h urine Ca, bronchoscopy, BAL, chest x-ray, pulmonary function tests, DLCO, thorax CT, and pathology. For Kveim test, a suspension of heat-sterilized splenic cells from patients with sarcoidosis (the Kveim-Siltzbach reagent) was used. A 0.15ml Kveim test suspension was injected into the volar aspect of the forearm intradermally. The injected area was biopsied six weeks later. Presence of the non-caseating granulomas in the biopsied samples was considered as a positive Kveim test reaction (1,2,3). The conventional laboratory and the Kveim test results were compared with respect to their contribution to a final accurate and definitive diagnosis concerning disease stages.

Laboratory results were designated as negative or positive for sarcoidosis diagnosis due to the normal physiologic normal or high level of the tests while imaging modalities comprised chest x-ray and thorax CT that were denominated as compatible or discordant with sarcoidosis. For an accurate evidence of sarcoidosis, presence of at least three conventional laboratory findings, compatible radiologic features, and pathologic data of the involved organs was required consistent with sarcoidosis along with the exclusion of diseases that may have similar clinical findings for differential diagnosis along. Primary objective of an accurate diagnosis was abutment of a compatible clinical and a radiologic profile with existence of non-caseating granulomatous inflammation in at least two organs. Kveim test was assessed as negative or positive for the presence of non-caseating granulomas in the biopsy samples.

Conventional laboratory and imaging findings were analysed under a single collaborated data input for their contribution to the definite diagnosis of sarcoidosis. Patient data and variables were presented as mean and standart deviations. For statistical analysis, SSPS version 21 was used.

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Kolmogrov Smimov, Shapiro Wilk tests, and Q-Q plot were performed to analyse a normal distribution. Pearson Chi-square test was used for adequate and Fisher's exact test was done for inadequate survey situations. For multiple comparisions, Bonferroni correction was utilized for the analysis of significant data. Spearman correlation was done for the assessment of data with an abnormal distribution. A p value of less than 0.05 was regarded as statistically significant. 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 (7).

Results

All patients had a definitive final sarcoidosis diagnosis. Sarcoidosis stage incidence of the patients is depicted in Table 1. Conventional laboratory

Table 1. Incidence of sarcoidosis stage.

Stage	Patient #	Incidence (%)
Stage 0	28	9.6
Stage I	132	44.0
Stage II	82	27.3
Stage III	46	14.0
Stage IV	12	4.0

comprising imaging and pathologic manifestations revealed compatible findings in 182 (60.7%) patients. Of these in whom a Kveim test was done, 224 (78%) patients had a positive result. Diagnostic yield of the conventional laboratory and the Kveim test findings relevant to disease stage is shown in Table 2 as a percentage among sarcoidosis patients. Statistical analysis concerning the correlation of sarcoidosis diagnosis for the conventional laboratory and the Kveim test comparison in regard to disease stage is revealed in Table 3. The sensitivity and the specificity of the test modalities along with the diagnostic yield of the collaborated approach is defined in Table 4.

Table 2. Diagnostic yield of the conventional laboratory and the Kveim test in regard to disease stage.

	Conventional laboratory		Kveim test	
Stage	**Pt #**	**Dx (%)**	**Pt #**	**Dx (%)**
Stage 0	10	34.5	20	62.1
Stage I	60	45.4	90	68.2
Stage II	68	82.9	71	86.6
Stage III	34	73.9	37	80.4
Stage IV	10	83.3	6	50.0
Total	182	60.7	224	78.0

Kveim test in sarcoidosis

The conventional laboratory test displayed a suggestive diagnostic yield for stages II, III, and IV of sarcoidosis. Kveim test revealed a significant diagnostic yield among all stages of sarcoidosis patients (Table 3). Kveim test exhibited a notable sensitivity in stage 0 sarcoidosis patients. Conventional laboratory corollary revealed a moderate revenue for the detection of active granulomatous inflammation due to distinctive results. The only diagnostic preponderance of the traditional laboratory methods over the Kveim test was noted as the stage IV sarcoidosis diagnosis provided by the visual eligibility of radiological imaging. Kveim test was not useful for the detection of extrapulmonary sarcoidosis to determine or identifiy specific organ involvement as the test only detected the presence of granulomatous inflammation (Table 4). According to the results of our study, Kveim test gave the most significant results for a definitive sarcoidosis diagnosis revealing a high sensitivity and specificity for the existence of active granulomatous inflammation for all stages of sarcoidosis. Conventional laboratory modalities demonstrated a better yield for detecting extrapulmonary organ involvement and for the discrimination of fibrotic disease.

Table 3. Correlation of the conventional laboratory and the Kveim test for discrepant aspects of sarcoidosis assessment.

	Conventional laboratory tests		Kveim test		Combined assessment of the laboratory and the Kveim tests	
	r	**p**	**r**	**p**	**r**	**p**
Active granulomatous inflammation	0.68	< 0.05	0.86	< 0.01	0.96	< 0.01
Extrapulmonary organ disease	0.72	< 0.05	0.54	< 0.05	0.92	< 0.01
Biopsy site identification	0.62	< 0.01	0.18	< 0.05	0.84	< 0.01
Discrimination of fibrotic and active parenchymal lung disease	0.86	< 0.01	0.42	< 0.05	0.78	< 0.01
Final definite diagnosis	0.64	< 0.05	0.86	< 0.01	0.98	< 0.01

Abbreviations: r: correlation coefficient; p: p value.

Table 4. Diagnostic sensitivity and specificity of the conventional laboratory, Kveim, and the integrated test modalities.

Diagnostic yield	Conventional laboratory tests	Kveim test	Integrated analysis of the laboratory and Kveim tests	p value
Sensitivity	%68.2	%76.4	%96.8	< 0.01
Specificity	%56.4	%72.8	%94.6	< 0.01

Kveim test in sarcoidosis

The conventional laboratory and the Kveim test results, revealed a significant yield for all aspects of sarcoidosis including diagnosis, extrapulmonary organ involvement, disease activity, and an accurate diagnosis (Table 3). The integrated analysis of our findings set forth an exclusively distinct sensitivity and specificity sarcoidosis diagnosis (Table 4). Each modality has exhibited a significant statistical output in terms of diagnosis, disease activity, and extrapulmonary organ involvement on its own revealing distinctive conclusions in different aspects of sarcoidosis.

Discussion

Kveim test is a suspension of splenic cells from sarcoidosis patients injected intradermally that has been in use worldwide for fifty years as a safe, simple specific technique to confirm the diagnosis of sarcoidosis, and to provide evidence of disease activity (6, 8-10). The test evokes a sarcoid granulomatous response in approximately four weeks similar to a tuberculin skin test. Kveim test is essentially a research tool due to its limited availability and storage of the reagent along with concerns about infectious disease transmission. We have retrospectively evaluated the diagnostic yield of the Kveim test in sarcoidosis patients relevant to disease stage. Kveim test was compared with the collaborated conventional approach comprising the laboratory and radiologic findings in terms of a definite diagnosis. Our results revealed that the Kveim test alone provided a significantly better diagnostic yield over the conventional laboratory tests. The potential of the Kveim test to discriminate between active granulomatous inflammation and fibrosis revealed more uncertain conclusions compared to the orthodox laboratory data analysis. Kveim test proclaimed more ambiguous and less significant results in detecting extrapulmonary organ involvement than the conventional approach which was more useful for the detection of specific organ site. Furthermore, collaborative assessment of the Kveim and the traditional laboratory test results achieved an accurate definite diagnosis in almost every patient beyond any doubt.

The highest diagnostic yield was obtained in stage II and III patients for the conventional and the Kveim test group of sarcoidosis patients. This is probably related to the intensity of granulomatous inflammation along with the burden of granulomas reaching the highest peak level of intensity and activity during these stages. On the other hand, the lowest diagnostic revenue for conventional laboratory group was found in stage 0 and I patients. Such a finding is relevant with the fact that the granulomatous inflammation is in its initial stages with a low granuloma burden along with the weak preliminary inflammatory activity that has not yet fully matured. Kveim test revealed a high yield in almost every stage of the disease, except stage IV. The low yield is probably caused by the diminishing the activity of granulomatous inflammation as a result of ongoing fibrosis that reduce the activity of granulomatous inflammation. This finding may also be associated with the low number of stage IV patients that may have influenced the power of statistical analysis adversely. For stage IV patients, the conventional laboratory findings revealed a more conclusive output owing to the contribution of HRCT that displayed pulmonary fibrosis accurately by its contribution for the detection of fibrotic pulmonary parenchyma of stage IV disease. This noteworthy acquisition is associated with the visual power of HRCT imaging in detecting pulmonary fibrotic disease. Kveim test did not reveal a statistically significant output for the detection of extrapulmonary organ sarcoidosis regardless of a single or multiple extrapulmonary organ involvement as it displayed positivity in both conditions. The conventional laboratory tests on the other hand set forth a distinctive conclusion for the detection of genuine organ disease due to unique results as the organ specific physical, laboratory, and imaging modalities have pointed out specific organ involvement that are probably relevant to the organ explicit manifestations.

There are some limitations concerning our study. The sample size for the assessment Kveim test is considerably high but studies with larger populations comprising patients with distinctive features will absolutely increase the power of statistical analysis. Second participants of our study were all of Caucasian origin that may have affected the manifestations of sarcoidosis due to the hereditary or genetic factors. Patients with distinctive and heterogenous racial features may reveal more definitive conclusions. Kveim test solution may have led to false negatives depending on the storage conditions and expiry dates (11) but utmost care with extreme caution has been paid for the supervision of these factors. Disease stability

or activity along with sarcoidosis stage due to the intensity of the granulomatous inflammation at the time of the implemented procedures may have influenced the results of the study. Positive Kveim test reaction may not be specific to sarcoidosis and may have been caused by fungal, or tuberculous infection (12,13) or inflammatory bowel disease (14) leading to false positive results. Such factors were excluded by an extremely attentive assessment during differential diagnosis. Immune paradox as the delayed type of hypersensitivity anergy in a setting of exuberant systemic granulomatous response is currently uncertain and relationship to the Kveim test is poorly understood (15). The paradox of cutaneous delayed type hypersensitivity anergy in a setting of intense immune response and the appearance of systemic granulomatous inflammation, indistinguishable from sarcoidosis, in persons with lymphohematogenous and solid neoplasms and a variety of cellular immune deficiencies (16,17) may emerge as the other drawbacks of the Kveim test. Presence of such diseases that may have adversely affected the Kveim test results was excluded in the differential diagnosis by an extremely meticulous assessment of our patients. Diagnostic yield of both test approaches may be associated with the sample size of each stage affecting the statistical analysis power particularly relevant to the low diagnostic yield of Kveim test in stage IV sarcoidosis patients.

The significant diagnostic yield of the Kveim test in stage 0 sarcoidosis patients compared to the conventional laboratory tests is the most definitive and distinctive conclusion of our study. The low diagnostic yield of the conventional laboratory modalities for stage 0 patients is due to the incipient granulomatous inflammation and the low granuloma burden in these patients that are Kveim test in sarcoidosis inadequate to be reflected or identified by the traditional modalities. Kveim test displays an exclusively high diagnostic yield compared to currently utilized conventional laboratory methods in almost every stage of sarcoidosis. The hallmark of the Kveim test is the achievement of a significant revenue with a single test but required an average of four weeks for diagnosis. As the sensitivity and specificity of the conventional laboratory modalities for sarcoidosis diagnosis are considered, Kveim test becomes the hallmark of sarcoidosis diagnosis. The second decisive and essential aspect of the Kveim test is its less variability according to the stages of sarcoidosis or granulomatous inflammatory phase compared to conventional laboratory procedures. The laboratory results displayed a relatively lower diagnostic yield in stages 0 and I while chest radiology, especially the thorax CT revealed the most significant diagnostic output for stage IV cases. Kveim test exhibited some uncertainty for discriminating active inflammation and fibrotic disease that is revealed by the lowest yield in stage IV patients. This phenomenon is probably due to the waning of active granulomatous inflammation replaced by fibrosis in stage IV patients denoting the more distinctive yield of the Kveim test during the ongoing inflammatory phase.

Disadvantages of the Kveim test appeared as the delayed results, storage conditions of the reagent, and the transmission probability of some infectious diseases. The high diagnostic yield with a single intervention emerged as the most outstanding feature of the Kveim test. For disease activity assessment, the Kveim test displayed more definitive results statistically compared to the conventional laboratory findings. This finding is probably be explained by the variable nature of the granulomatous inflammation relevant to disease stages. For extrapulmonary organ involvement the conventional modalities showed a better diagnostic yield than the Kveim test as it revealed positivity without differentiating extrapulmonary organ disease while the traditional approach identified organ specific results due to the specific organ related results. Physical examination in cutaneous or ocular involvement and the imaging modalities such as ultrasonography or CT in liver, spleen, and lung sarcoidosis had a significant diagnostic contribution. When the conventional laboratory data and Kveim test results were incorporated, a definitive accurate diagnosis of sarcoidosis was achieved almost in all patients.

Conclusions

Kveim test revealed a statistically significant diagnostic yield among all stages of sarcoidosis for definite diagnosis. As a single test, it provided a great advantage for diagnosis compared to the conventional laboratory modalities. Kveim test was unable to identify pulmonary fibrotic disease and extrapulmonary organ involvement as it revealed positivity in all stages whether fibrosis or extrapulmonary organ disease was present. Conventional laboratory analysis displayed a better yield for the detection of extrapulmonary organ involvement and lung fibrosis.

These findings are associated with the organ exclusive corollary and the potential visual power of thorax CT that detected pulmonary fibrosis. Although it may be considered as an old fashioned, forgotten, or even a discredited diagnostic procedure and despite its low sensitivity for identifying extrapulmonary organ sarcoidosis and pulmonary fibrosis, the Kveim test precision for a definite sarcoidosis diagnosis can never be overlooked or underestimated. On the other hand, combined assessment of the conventional laboratory and the Kveim test led to an accurate diagnosis beyond any reasonable doubt among all stages of sarcoidosis.

Author Contributions: CT designed and wrote the manuscript. EY uploaded the patient findings and data to the study. MB prepared the laboratory findings of the patients. HY analyzed the Kveim test results. ÜK performed the statistical analysis.

Conflicts of Interest: The authors declare that they do not have not any conflicts of interest to declare associated with this study. We as authors state explicitly that any kind of potential conflicts do not exist.

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