Utility of Screening Investigations for Systemic Sarcoidosis in Undifferentiated Uveitis

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• PURPOSE: To establish the utility of screening investigations for systemic sarcoidosis in a large cohort of subjects presenting with undifferentiated uveitis.
• DESIGN: Evaluation of a diagnostic test.
• METHODS: Retrospective review of consecutive subjects presenting to Auckland District Health Board with undifferentiated uveitis who underwent screening for sarcoidosis.
• RESULTS: Seven hundred nine subjects were included in the study. Systemic sarcoidosis was identified in 10.7%, and was biopsy proven in 43.4%. Sensitivity and specificity were highest for computed tomography (CT) of the chest (98.0% and 100%) and for chest radiograph (CXR; 57.6% and 100%). Serum ACE was elevated in 43 subjects, of whom 29 (67.4%) had systemic sarcoidosis. Sensitivity of serum ACE was 38.2% and specificity 97.8%, with an area under the curve (AUC) of 0.801. Lymphopenia was observed in 40 subjects, of whom 18 (45.0%) had systemic sarcoidosis. Sensitivity of lymphopenia was 23.7%, with specificity 96.5% and AUC 0.761. All subjects with elevated ACE and lymphopenia had evidence of systemic sarcoidosis. Biopsy was performed in 50 subjects, positive in 33 subjects (66.0%). Mediastinal biopsy was the most frequent (26 subjects). Skin biopsy was performed in 11 subjects (positive in 8). Only 1 subject with a positive skin biopsy had elevated ACE, lymphopenia, and bihilar lymphadenopathy on CXR.
• CONCLUSIONS: Sensitivity and specificity were highest for chest CT. Although CXR had excellent specificity, CXR screening alone would still miss many cases of sarcoidosis. Combined elevated ACE and lymphopenia were strongly suggestive of systemic sarcoidosis, and biopsy of skin lesions may detect patients otherwise missed by routine screening tests. (Am J Ophthalmol 2019;206:149–153. © 2019 Elsevier Inc. All rights reserved.)

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SARCOIDOSIS IS A MULTISYSTEM SYSTEMIC DISORDER, characterized histologically by noncaseating granulomas. It most commonly presents with involvement of the lungs or mediastinal lymph nodes, but may have liver, cardiac, joint, skin, neurologic, and eye manifestations. Five percent to 20% of subjects with systemic sarcoidosis have eye involvement, most commonly dry eye or uveitis.[1]

Sarcoidosis is common in subjects presenting to uveitis clinics, occurring in 5% to 7% of subjects seen in general uveitis clinics.[2,3] Only one-third of those with sarcoidosis present with a known history of disease, and often it is left to the ophthalmologist to suggest the diagnosis and refer appropriately.[4] The clinical features of sarcoid uveitis have been defined by the International Workshop on Ocular Sarcoidosis, and may include (1) mutton fat keratic precipitates, small granulomatous keratic precipitates, and/or iris nodules; (2) trabecular meshwork nodules and/or tent-shaped peripheral anterior synechiae; (3) vitreous opacities displaying snowballs, strings, or pearls; (4) multiple chorioretinal peripheral lesions; (5) nodular and/or segmental periphlebitis and/or retinal macroaneurysm in an inflamed eye; (6) optic disc granuloma and/or solitary choroidal nodule; and (7) bilaterality.[5] However, a recent study of 884 uveitis patients, including 180 with systemic sarcoidosis, has shown that only 64% have 3 or more signs positive, and 10% will either have no typical clinical signs or only bilateral disease.[6] Clinical history is valuable, and investigations may include serum angiotensin converting enzyme (ACE), full blood count, chest radiograph (CXR) or computed tomography (CT) of the chest.

The aim of this study was to explore the reliability of serum ACE, lymphopenia, CXR, and chest CT in the diagnosis of systemic sarcoidosis in subjects with undifferentiated uveitis.

METHODS

• SUBJECT SELECTION: Consecutive subjects aged ≥16 years presenting with undifferentiated uveitis to the Department of Ophthalmology, Auckland District Health Board, between January 1, 2008, and December 31, 2016, undergoing measurement of serum ACE were included for retrospective analysis. This study received approval from the Research Development Office at Auckland District Health Board (A+7423) and adhered to the tenets of the

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Declaration of Helsinki. Subjects with known systemic disease associated with uveitis at presentation, and those with a clinical presentation typical for a specific condition (such as toxoplasmosis or Fuchs heterochromic iridocyclitis) were excluded, as were subjects currently using ACE inhibitors. The subjects were screened according to a standardized protocol, with all subjects offered full blood count, C-reactive protein, serum ACE, syphilis serology, and CXR, with other tests such as HLAB27, quantiferon TB gold, β2 microglobulin, performed where clinically relevant. Subjects in whom the clinical suspicion of sarcoidosis was high were referred to a respiratory physician specializing in sarcoidosis for further investigation. High-resolution chest CT was performed where the index of suspicion for sarcoidosis was considered high by a uveitis consultant (J.S. or R.N.) or by the respiratory physician, before the commencement of systemic immunosuppression.

Biopsy was offered for all subjects with lung lesions in whom there was considered to be diagnostic uncertainty (at the discretion of the respiratory physician) and for those with skin lesions or enlarged peripheral lymph nodes amenable to biopsy.

In the absence of any positive findings on systemic workup, subjects were considered to have idiopathic disease.

• **DATA COLLECTION:** Clinical notes were reviewed for all subjects to document demographics, clinical presentation, and final diagnosis. All subjects with a clinical presentation and/or screening investigations suggestive of systemic sarcoidosis were referred to a physician for further assessment and investigation.

Serum ACE levels were considered positive if they were elevated >2 standard deviations (SDs) above the mean reference value for our laboratory (>68 U/L). Lymphocyte levels were considered low if they were $<1.0 \times 10^9$/L.[7]

CXRs were reported by an experienced radiologist and considered consistent with sarcoidosis in the presence of bihilar lymphadenopathy. Other findings suggestive of possible sarcoidosis, such as unilateral hilar lymphadenopathy, pulmonary nodule, or signs of interstitial lung disease, were considered equivocal and were investigated further with chest CT.

• **ANALYSIS AND STATISTICS:** Data were analyzed in SPSS statistical software, version 25 (IBM, Armonk, NY, USA). Continuous data are presented as median (interquartile range [IQR]), and categoric data are presented as number (%). Sensitivity, specificity, positive predictive value, and negative predictive value were calculated. Receiver operating characteristic curves were plotted for serum ACE and lymphocyte count, and area under the curve (AUC) reported. An AUC of 1.0 is a perfect test, 0.9–1.0 is considered excellent, 0.8–0.9 is good, 0.7–0.8 is fair, 0.6–0.7 is poor, and <0.6 is worthless. All tests were 2-tailed and a *P* value of <.005 was considered significant.

TABLE 1. Anatomical Classification of Uveitis and Association With Systemic Sarcoidosis

Anatomical Classification	Number	Systemic Sarcoidosis, %
Acute anterior uveitis	330	2.7
Chronic anterior uveitis	131	13.7
Intermediate uveitis	101	15.8
Panuveitis	138	25.4
Posterior uveitis	52	9.6

Note some subjects had acute or chronic anterior uveitis and intermediate uveitis.

RESULTS

A TOTAL OF 709 PATIENTS WITH UNDIFFERENTIATED UVEitis underwent screening for systemic sarcoidosis during the study period. The median age was 47.1 years (IQR 34.7–61.5), and 51.8% were female. Acute anterior uveitis was the most common presentation in 330 subjects (46.5%), followed by chronic anterior uveitis in 131 subjects (18.5%), intermediate uveitis in 101 subjects (14.2%), panuveitis in 138 subjects (19.5%), and posterior uveitis in 52 subjects (7.3%). Involvement was bilateral in 324 subjects (45.7%). Systemic sarcoidosis was identified in 76 subjects (10.7%), and was biopsy positive in 33 subjects (43.4%). Frequency of sarcoidosis by anatomical classification of uveitis is reported in Table 1. Sarcoidosis was most common in those with panuveitis, intermediate uveitis, or chronic anterior uveitis.

Sensitivity, specificity, and positive and negative predictive values of screening investigations are reported in Table 2.

Serum ACE was elevated in 43 subjects (6.1%), of whom 29 (67.4%) had systemic sarcoidosis. Median serum ACE was 56.7 (IQR 42.2–89.1) in subjects with systemic sarcoidosis, compared to 31.5 (IQR 19.5–41.8) in those with no evidence of sarcoidosis. The receiver operating characteristic curve for serum ACE is shown in Figure 1, with an AUC of 0.801.

CXR was abnormal in 107 subjects (15.1%). Thirty-eight subjects demonstrated bihilar lymphadenopathy. A further 14 subjects had changes considered equivocal for sarcoidosis, including unilateral hilar lymphadenopathy, pulmonary nodule, or interstitial lung disease. Of these, 10 were found to have systemic sarcoidosis on further investigation. Sixteen subjects had apical scarring, suggestive of possible previous tuberculosis infection. The most common other abnormalities included increased cardiothoracic ratio in 11 subjects, and mild congestive heart failure in 5 subjects. One subject demonstrated pulmonary metastasis. In the subjects with normal CXR who were subsequently diagnosed with sarcoidosis, 92.3% had bilateral disease and 53.8% had panuveitis. More than half (57.7%)

TABLE 2. Reliability of Screening Investigations for Systemic Sarcoidosis

Investigation	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Serum ACE	38.2	97.8	67.4	92.9
Lymphopenia	23.7	96.5	45.0	91.3
CXR	57.6	100	100	94.4
Chest CT	98.0	100	100	98.2

ACE = angiotensin converting enzyme; CXR = chest radiograph; CT = computed tomography; PPV = positive predictive value; NPV = negative predictive value.

Equivocal results for CXR (n = 14) and chest CT (n = 17) excluded.

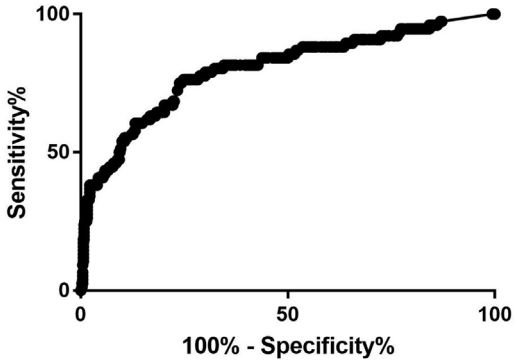

FIGURE 1. Receiver operating characteristic (ROC) curve for serum ACE. Area under curve (AUC) = 0.801.

underwent chest CT—all of which were abnormal, with bihilar lymphadenopathy in 73.3% and pulmonary nodules or mediastinal lymphadenopathy in the remainder. The subjects who did not undergo chest CT in this group were all diagnosed by positive skin biopsy. Serum ACE was elevated in 34.6% and lymphopenia was observed in 38.5% of this group.

Comparing the utility of CXR to serum ACE in screening, CXR had a higher sensitivity and specificity than serum ACE (Table 2). Of those subjects ultimately diagnosed with systemic sarcoidosis, 16 subjects had elevated ACE and bihilar lymphadenopathy on CXR; 22 subjects had bihilar lymphadenopathy with a normal serum ACE; 10 subjects had elevated serum ACE with a normal CXR; 10 subjects had equivocal changes on CXR (7 with elevated ACE, 3 with normal ACE); and 18 subjects with systemic sarcoidosis had a normal CXR and normal serum ACE.

Chest CT was performed in 129 subjects and was abnormal in 93 (72.1%). Fifty subjects had a CT appearance consistent with sarcoidosis. A further 17 subjects had signs that were equivocal for sarcoidosis on chest CT, including unilateral hilar lymphadenopathy, pulmonary nodule, or interstitial lung disease. Of these, 9 were found to have systemic sarcoidosis on further investigation. Fifty-eight subjects with a normal CXR underwent chest CT. Eleven of these showed bihilar lymphadenopathy on CT, and a further 9 showed changes that were equivocal for sarcoidosis, prompting further investigation.

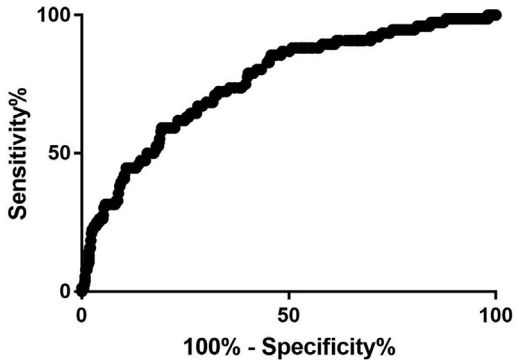

FIGURE 2. Receiver operating characteristic (ROC) curve for lymphopenia. Area under curve (AUC) = 0.761.

Lymphopenia was observed in 40 subjects (5.6%), of whom 18 had systemic sarcoidosis (45.0%). Lymphopenia was noted in 23.7% of those with systemic sarcoidosis, compared to 3.5% of those with no evidence of sarcoidosis. Median lymphocyte count was 1.4 (IQR 1.0–1.9) in subjects with systemic sarcoidosis, compared to 2.0 (IQR 1.6–2.6) in those with no evidence of sarcoidosis. The receiver operating characteristic curve for lymphopenia is shown in Figure 2, with an AUC of 0.761. All subjects with both lymphopenia and elevated ACE were found to have sarcoidosis in this sample.

Biopsy was performed in 50 subjects, positive for sarcoidosis in 33 and inconclusive in 2 subjects. Biopsy sites included mediastinal lymph nodes and/or lung 26 subjects; skin biopsy 11; cervical lymph nodes 4; liver 2; and then individual subjects with biopsies from the following sites—breast, cardiac, conjunctiva, lacrimal gland, orbit, retina, and supraclavicular lymph node. In 1 subject, initial biopsy of a tattoo margin showed an inflammatory reaction with no granulomas; however, subsequent skin biopsy (of a nontattoo area) was consistent with sarcoidosis.

Looking in more detail at those receiving skin biopsy, biopsy was positive in 8 subjects (72.7%). Only 1 of these subjects had elevated serum ACE, lymphopenia, and bihilar lymphadenopathy on CXR (12.5%).

DISCUSSION

THE CURRENT STUDY DESCRIBES THE SENSITIVITY AND specificity of serum ACE, lymphopenia, CXR, and chest CT in the diagnosis of systemic sarcoidosis in subjects with undifferentiated uveitis. Significant debate exists

about the preferred screening for sarcoidosis, with some specialists advocating CXR as the primary screening method[8] and a study by Kaiser and associates demonstrated the value of chest CT in subjects previously deemed "idiopathic."[9] The current study demonstrated that chest CT has the best sensitivity and specificity for sarcoidosis; however, this must be weighed carefully against the risks of radiation exposure and the costs involved in screening a large number of healthy individuals.[10,11,12] In our center over the study period we recommended chest CT to all patients with abnormalities demonstrated on CXR, and also to most patients with ocular features highly suspicious for sarcoidosis.

CXR performed well at diagnosing subjects with systemic sarcoidosis, with a sensitivity of 57.6% and a specificity in the current study of 100%. A further study by Acharya and associates has documented a similar result, with sensitivity of 68% and specificity 96% for CXR.[6] Care must be taken in interpreting this high specificity, however, as subjects have been seen with reported bihilar lymphadenopathy that are later diagnosed as tuberculosis or lymphoma following biopsy. Wherever possible, biopsy is still recommended to confirm the diagnosis.[5] The additional advantage of screening with CXR is the ability to pick up other lesions, in particular, evidence of previous tuberculosis infection as seen in 16 subjects in the current study.

Serum ACE was first reported to be elevated in systemic sarcoidosis in 1975, and elevated serum ACE forms part of the diagnostic criteria for sarcoid uveitis.[5,13] Within the current study, serum ACE had a sensitivity of 38.2%; however, specificity was high (97.8%) and two-thirds of subjects with elevated serum ACE were observed to have systemic sarcoidosis on investigation. Serum ACE has an additional benefit, in that when elevated, it can be used to monitor subsequent disease activity.[14] The utility of serum ACE in the detection of systemic sarcoidosis has recently been examined in a large study from Moorfields, United Kingdom.[15] In this study, the sensitivity of serum ACE was higher (78.1%); however, the cutoff value for elevated serum ACE was 52. The current study used a cutoff of 68 for elevated serum ACE, based on the distribution of normal values reported by the local laboratory. It may be that lowering the threshold would allow greater identification of cases, albeit at the expense of more false positives. It is important to remember that serum ACE will be low in subjects on ACE inhibitors. Measurement of serum lysozyme has been advocated for this group; however, this was not available at our center, and thus subjects on ACE inhibitors were excluded from analysis.

Lymphopenia was initially described in connection with sarcoid uveitis by Jones and associates in a retrospective case-control study of 112 subjects with sarcoidosis-associated uveitis, compared to 398 controls with other forms of uveitis.[7] They observed lymphopenia in 26.8% of subjects with sarcoidosis associated uveitis, compared with only 6.0% of those with other diagnoses. The current study observes a similar association, with lymphopenia in 23.7% vs 3.5%. The AUC for lymphopenia was 0.761 in the current study, so it did not perform as well as serum ACE in distinguishing systemic sarcoidosis. However, in those with lymphopenia and elevated serum ACE, the risk of systemic sarcoidosis becomes very high. The current study supports the inclusion of lymphopenia in the upcoming diagnostic criteria for sarcoid uveitis.

A further finding from this study is the importance of highlighting the value of skin biopsy in subjects with rash suspicious for sarcoidosis. Skin biopsy was positive for sarcoidosis in 72.7% of those biopsied, and such patients could otherwise have been missed, with only 1 subject showing elevated ACE, lymphopenia, and abnormal CXR.

Subjects with sarcoidosis may be at risk for progressive interstitial lung disease that can benefit from early intervention, and also at risk for cardiac death from arrythmias.[16] At the time this study was conducted, we did not routinely include electrocardiography looking for conduction defects as part of our diagnostic evaluation. The benefit of diagnosing sarcoidosis (particularly in otherwise asymptomatic individuals) must be weighed against the risk and cost of additional testing. Diagnosis of sarcoidosis has a prognostic benefit to subjects[17] and can help eliminate alternative diagnoses, including tuberculosis and lymphoma.

This study demonstrates the utility of screening investigations in systemic sarcoidosis to aid interpretation of positive and negative test results. In particular, it demonstrates a high sensitivity and specificity for chest CT and CXR. In addition, it demonstrates that screening with CXR alone will miss a number of cases, and consideration should also be given to adding blood tests, chest CT, and/or skin biopsy in suspicious cases. A combined elevated ACE and lymphopenia was strongly suggestive for systemic sarcoidosis, and skin biopsy of rash may pick up those in whom other screening investigations may be negative.

ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST and none were reported. The authors indicate no financial support or financial conflict of interest. All authors attest that they meet the current ICMJE requirements to qualify as authors.

No conflicting relationship exists for any author.

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