Histoplasma Exposure Risk Assessment in Sarcoidosis Patients and Its Correlation with Calcified Lymphadenopathy: A Case Control Study

P. Sen, MD[1], M. Azam[2], T. Kwiatkowski[3], J. H. Jennings, MD[1]

1. Division of Pulmonary & Critical Care Medicine, Henry Ford Hospital, Detroit, MI

2. College of Engineering, Michigan State University, Detroit, MI,

3. College of Engineering and Science, University of Detroit, Detroit, MI,

Abstract

RATIONALE: Hilar and mediastinal lymphadenopathy is a common and an often isolated finding in sarcoidosis. Calcification in these nodes are less frequently found in sarcoidosis and its significance is unknown. Nodal and visceral calcification has been classically described in histoplasmosis, raising a concern whether the presence of calcified lymphadenopathy (LAD) in patients diagnosed with sarcoidosis may actually be secondary to histoplasma exposure.

METHODS: This was an institutional case-control study of outpatients at Henry Ford Hospital, Michigan. Patients diagnosed by a pulmonologist with sarcoidosis and who had a CT Scan of Thorax performed between July 1, 2012 to June 30, 2016 were included. A questionnaire was administered by phone; it was designed to elicit exposures to known risk factors for histoplasmosis: history of living on farms, wood chopping, professional construction work or carpentry, land tilling and regular gardening. Interviewers were blinded to the calcification status on CT. Responses were recorded either in the affirmative or negative. Scores for the questionnaire ranged from 0 to 5.

RESULTS: 141 patients were screened. 54 patients consented to the interview, 39 of which (72%) had no calcification and 15 (28%) had calcifications. Overall, patients with calcified LAD had a higher median total exposure score (1 [95% CI 0-2] than those without (0 [95% CI 0-1]) (p=0.023). Individual items showed that living on farms was those most significant risk factor for calcified LAD (adjusted OR 25.5 [95% CI 3.3 to 198.3], p = 0.002). Though there was a positive trend in some of the other risk factors, they weren't statistically significant.

CONCLUSIONS: This study shows that in patients who carry a diagnosis of sarcoidosis, a detailed risk assessment should be made for Histoplasma exposure, particularly for those patients with calcified LAD. Of the different exposures queried, a history of living on farms was a strong risk factor for the presence of calcified lymphadenopathy in sarcoid patients.

1. Introduction

Hilar and mediastinal lymphadenopathy is a common and an often isolated finding in sarcoidosis[1]. Calcification in these nodes are less frequently found in sarcoidosis and is associated with duration of disease.[2] Nodal and visceral calcification has been classically described in histoplasmosis[3]. This raises a concern whether the presence of calcified lymphadenopathy (LAD) in patients diagnosed with sarcoidosis may truly be secondary to Histoplasma exposure. Our objective was to assess the risk of histoplasma exposure in patients diagnosed with sarcoidosis and its correlation with calcification of intra thoracic lymph nodes

2. Methods

This is an institutional case-control study performed at Henry Ford Hospital, Michigan.

All outpatients seen between July 1, 2012 to June 30, 2016 were screened. Inclusion criteria was a diagnosis of sarcoidosis, established by a pulmonologist and documented in their clinic notes, and had a CT scan of thorax performed during the study period. The first CT, if multiple available, was the index CT.

Patients were excluded if they did not have a CT, or if there was no hilar/mediastinal adenopathy.

CT's were scored in a blinded fashion and recorded as calcified or non-calcified.

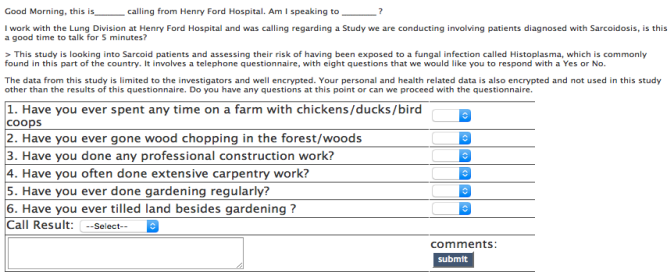
We contacted the patients by phone and administered a questionnaire to elicit a history of six common histoplasmosis exposures : history of living on farms, wood chopping, professional construction work, regular carpentry, land tilling and regular gardening.

Interviewers were blinded to the calcification status on CT. Responses were recorded either in the affirmative or negative with 0 and 1. Total Scores for the questionnaire ranged from 0 to 6.

Statistical Analysis

Continuous variables were compared using the Student t test or the Kruskal-Wallis rank-sum test in the cases of nonnormally distributed variables and expressed, respectively, as means ± sd or median and interquartile range. Categorical variables were expressed as percentages and analyzed using a chi square. logistic regression analysis was used to assess various exposure risks as predictors of having calcification on CT.

[


Good Morning, this is_____ calling from Henry Ford Hospital. Am I speaking to _____ ?

I work with the Lung Division at Henry Ford Hospital and was calling regarding a Study we are conducting involving patients diagnosed with Sarcoidosis, is this a good time to talk for 5 minutes?

> This study is looking into Sarcoid patients and assessing their risk of having been exposed to a fungal infection called Histoplasma, which is commonly found in this part of the country. It involves a telephone questionnaire, with eight questions that we would like you to respond with a Yes or No.

The data from this study is limited to the investigators and well encrypted. Your personal and health related data is also encrypted and not used in this study other than the results of this questionnaire. Do you have any questions at this point or can we proceed with the questionnaire.

1. Have you ever spent any time on a farm with chickens/ducks/bird coops
2. Have you ever gone wood chopping in the forest/woods
3. Have you done any professional construction work?
4. Have you often done extensive carpentry work?
5. Have you ever done gardening regularly?
6. Have you ever tilled land besides gardening ?

Call Result: --Select--

comments:

submit

Figure 1. Telephone Questionnaire

3. Results

141 patients were screened to be eligible and included in the study. Out of these 35 patients were deceased, 34 could not be reached and 18 refused to answer the questionnaire.

Of those who answered, 39 (72%) had no calcification and 15 (28%) had calcified lymphadenopathy.

Overall, patients with calcified LAD had a higher median total exposure score (1 [95% CI 0-2] than those without (0 [95% CI 0-1]) (p=0.023).

A logistic regression analysis showed that living on farms with poultry was the most significant risk factor for calcified lymphadenopathy, controlled for the other factors.(Adjusted OR 25.5 [95% CI 3.28 to 198.3], p = 0.002). Though there was a positive trend

Table 1 Baseline Characteristics

	Calcified LAD (n=41)	Non calcified LAD (n=100)	P value
African American n (%)	28 (69.3)	72 (72)	
Sarcoid Stage, (%)			0.261
0	5 (12.2)	15 (15)	
1	4 (9.8)	18 (18)	
2	4 (9.7)	19 (19)	
3	9 (22)	17 (17)	
4	19 (46.3)	31 (31)	
Mean DLCO (% predicted)	58.2 (19.7)	66.3(18.8)	0.248

Table 2. Predictors of calcified lymphadenopathy

	Adjusted Odds Ratio	95% CI	P value
Living on farm	25.52	3.28 – 198.3	0.002
Wood chopping	0.36	0.03- 4.96	0.013
Construction	0.04	0.00-0.51	0.248
Carpentry	2.34	0.09 – 60.1	0.608
Gardening	3.98	0.64 – 24.8	0.138
AA race	2.60	0.46 – 14.7	0.279

in some of the other risk factors, they weren't statistically significant.

4. Discussion

Sarcoidosis is often a diagnosis of exclusion despite its characteristic epidemiologic, radiologic and histopathologic features. The commonest differential includes other granulomatous diseases including fungal infections.

In the "Histoplasma belt" which includes Michigan, histoplasmosis becomes an important diagnosis to exclude. There is also conjecture of histoplasmosis triggering an immune reaction akin to sarcoidosis.

As early as 1989, Wheat et al described 11 cases of sarcoidosis proven to have underlying Histoplasma infection.[4] There have been numerous case reports since describing presence of histoplasmosis in patients diagnosed with sarcoid.

Diagnosing Histoplasmosis, particularly a chronic infection or a remote exposure can be difficult. Urinary antigen has a sensitivity around 93% but lower in chronic cases.[5] A more sensitive and specific molecular marker, Hcp 100 gene can be measured using PCR[6]

All the above tests would increase test and expense burden necessitating a screening method. Presence of lymph node and visceral calcification should trigger suspicions. Our study shows a strong correlation

between calcifications and a history of growing up in farms around poultry. The presence of both may warrant advanced testing before establishing a diagnosis of sarcoidosis.

5. References

1. Baughman, R.P., et al., *Clinical characteristics of patients in a case control study of sarcoidosis.* Am J Respir Crit Care Med, 2001. **164**(10 Pt 1): p. 1885-9.
2. Miller, B.H., et al., *Thoracic sarcoidosis: radiologic-pathologic correlation.* Radiographics, 1995. **15**(2): p. 421-37.
3. Gurney, J.W. and D.J. Conces, *Pulmonary histoplasmosis.* Radiology, 1996. **199**(2): p. 297-306.
4. Wheat, L.J., M.L. French, and J.L. Wass, *Sarcoidlike manifestations of histoplasmosis.* Arch Intern Med, 1989. **149**(11): p. 2421-6.
5. Hage, C.A., et al., *A multicenter evaluation of tests for diagnosis of histoplasmosis.* Clin Infect Dis, 2011. **53**(5): p. 448-54.
6. Toranzo, A.I., et al., *[Molecular diagnosis of human histoplasmosis in whole blood samples].* Rev Argent Microbiol, 2009. **41**(1): p. 20-6.