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Comparison between diffuse and partial involvement of thoracic lymph nodes on the outcome of sarcoidosis patients

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Abstract. *Background and aim:* Sarcoidosis is a systemic disease of unknown etiology with diverse clinical manifestations. Disease may resolve spontaneously or require immunosuppression to control progression. Currently, there is no predictive model to direct treatment, and management is guided by symptoms and functional impairment. This study examines the association between biopsy features and prognosis. *Methods:* This is a retrospective population-based cohort study. New cases of biopsy-proven sarcoidosis were divided into two groups: those with diffuse thoracic lymph nodes (TLN) involvement, versus partial TLN involvement (Defined as Non-necrotizing granuloma (NNG) found in some but not all sampled TLN). We compared outcomes one year after diagnosis. We assessed the need for immunosuppression, the number of hospitalizations, and lung function deterioration. *Results:* 77 cases were included in the final analysis. 48.1% demonstrated extensive TLN involvement, and 51.9% demonstrated partial or non-involvement of sampled TLN. The partial positive group had a more aggressive disease, reflected by a significantly higher need for steroid therapy in the first year after diagnosis (45.0% vs. 18.9% p=0.015). The number of hospitalizations and lung functions were not significantly different between groups. *Conclusions:* Our findings demonstrate a significantly increased need for steroidal therapy among sarcoidosis patients with a partial positivity of TLN. These findings suggest that the degree of TLN involvement can help predict worse outcome and guide therapeutic decisions.

Key words: sarcoidosis, EBUS, non-necrotizing granulomas

Introduction

Sarcoidosis is a systemic disease of unknown etiology with many clinical presentations that can adversely affect almost any body system (1,5). The most common manifestation is thoracic lymph node (TLN) enlargement and interstitial pulmonary disease (2). Pulmonary disease is responsible for most of the morbidity and mortality in sarcoidosis (3,4).

The pulmonary prognosis and treatment of sarcoidosis vary amongst patients and are directed by radiological stage (6), combined with the severity of symptoms and functional impairment (7). Poor prognosis may be reflected by a decline in lung function, repeated hospitalizations, progressing fibrosis, or failure to withdraw steroids treatment (3).

Several studies tried to identify predictors of poor outcomes (4). Radiological stage at presentation is usually correlated with prognosis. Patients who presented at stage 1 usually recover spontaneously without treatment (50%-90%), while patients in more advanced stages (stages 3-4) have a lower chance to recover (less than 30%), even with adequate treatment (3). Radiological stage based on a high-resolution CT might yield better prediction (9), however, there are many exceptions to this rule (4).

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Patients with sarcoidosis may experience an accelerated decline in lung function, irrespective of symptoms or disease stage at presentation (8) suggesting lack of validated tool to predict outcomes and guide treatment (10).

Most patients with sarcoidosis have hilar and mediastinal lymphadenopathy. Currently, EBUS-TBNA (Endobronchial ultrasound-guided transbronchial needle aspiration) is the preferred method for tissue sampling (11), with an excellent diagnostic yield of 87% (95% CI, 94–91%) (12)(13). The formation of non-necrotizing granuloma (NNG) is the hallmark of sarcoidosis (14). It is an accumulation of inflammatory cells, mainly lymphocytes, in response to antigen presentation interceded by macrophage and CD4 cells (15). Many nodes contain the typical NNG therefore considered positive, while others demonstrate normal lymphoid tissue (16). The extent of TLN involvement might serve as a window to the aggressiveness of the disease, with difference in tissue infiltration representing different trajectories. The study aims to compare disease outcomes after a one-year follow-up between patients with diffuse involvement of TLN and partial involvement. If the degree of TLN is indicative of future outcome, this data could assist in patient management immediately after the diagnosis of sarcoidosis was made.

Materials and methods

Study setting

This was a retrospective cohort study. We included all new cases of definitive sarcoidosis who underwent EBUS-TBNA as part of their work-up at Soroka University Medical Center (SUMC) between Jan 1, 2016, and Dec 31, 2020. Definitive sarcoidosis was considered if senior pulmonologist confirmed the diagnosis after six months following the initial biopsy. Patients with alternative diagnoses (e.g., TB/NTM, lymphoma, vasculitis, etc.), as well as patients with solid-organ or hematologic malignancy were excluded. Subjects meeting enrollment criteria were further divided into one of two study groups based on the extent of TLN positivity. Only patients with all inclusive NNG positivity entered the extensive TLN group.

EBUS-TBNA was done under sedation with a combination of propofol, midazolam, and opioids. All patients underwent a complete visual evaluation of accessible nodes using a convex probe endobronchial ultrasound (EBUS) scope (BF-UC180, Olympus medical systems, Japan). Biopsy was done with Vizishot I or II EBUS/TBNA needle 21 or 22 Gauge (Olympus Medical Systems, Japan). The most suspected and easily accessible nodes were selected for tissue sampling. The number of sampled TLN stations was for the operator's discretion. It was advised to sample at least two different nodal stations, as this increases the diagnostic yield (17). Biopsy was done with Vizishot I or II EBUS/TBNA needle 21 or 22 Gauge (Olympus Medical Systems, Japan). In addition, conventional bronchoscopy including trans-bronchial biopsy (TBB) or endobronchial biopsy (EBB), was done when clinically appropriate. TLN aspirates underwent cell block processing and analysis. Each sample was processed independently by a local cytologist. In addition, tissue samples were sent in routinely for Ziehl–Neelsen staining, as well as culture and PCR testing for Mycobacterium tuberculosis.

Data collection

Data was collected from the SUMC computerized database. Our team reviewed the files manually and collected relevant data. LN parameters (e.g., number of enlarged LN, size (short axis), location of sampled TLN) were taken from EBUS report. Radiologic stage was with a CT image. Data was transferred to the computing unit for crossing and complementary clinical data (Demographic data, disease manifestation, etc.) and was returned as an anonymized and centralized file for statistical processing.

Statistical analysis

For the univariate analysis, we applied an unpaired t-test for comparing two normally distributed groups and ANOVA for multiple groups. Mann Whitney for two non-normally distributed groups and Chi-square for categorical variables. Outcomes were assessed one year after diagnosis. Study outcomes were defined as the need for oral steroidal treatment (Prednisone- ATC H02AB07) during the year, the number of hospitalizations during the year, and lung function measured in 10-13 months after diagnosis. For outcomes that were significantly

different between groups, we conducted a multivariable logistic regression to estimate the adjusted odds ratio (OR). Potential confounders were included in the model based on preceding univariable analysis comparing patients who received steroidal treatment a year after diagnosis and patients who didn't. The significance level has been set to 5% in two-sided testing. Percentages have been rounded to one decimal. Data were analyzed using SPSS 25.0.

Results

We identified 147 cases that presented with NNG in TLN sampling between Jan 1, 2016, and Dec 31, 2020. After reviewing the medical files, we excluded 70 cases, mainly due to uncertainty in diagnosis or concomitant malignancy. Seventy-seven cases were included in the final analysis, with 37 cases (48.1%) demonstrating diffuse positivity of TLN in their pathological findings and 40 cases (51.9%) in the partial positivity group.

The mean age at diagnosis was 56.4 (SD ±13.7) with 49.4% male. The most common radiological stage was 2 (n=48, 62.3%), and the mean size of the largest TLN was 15.9 mm (SD ±5.4). For comorbidity assessment, we use Charlson Comorbidity Index (CCI) with age consideration, with a mean of 2.87 (SD ±2.4). A comparison of demographic characteristics, variables of disease manifestation, and sampling features is presented in Table 1. A smoker was defined as a patient whose medical records contain positive smoking status even if not currently smoking. The smoker rate was higher in the diffuse TLN positive group (45.7% vs. 15.0% p=0.004). Other demographic characteristics were similar between groups.

Respiratory symptoms, including dyspnea and cough, were significantly more common in the partial positive TLN group (67.5% vs 43.2% p=0.032) while other symptoms such as fever, fatigue, and weight loss were equivalent. Radiological staging, spirometry, Blood tests and other clinical manifestations were

Table 1. Comparison between diffuse and partial involvement of lymph nodes. The percentage is exhibited ignoring missing data.

Involvement degree	**Partial positivity N= 40 (51.9%)**	**Diffuse positivity N=37 (48.1%)**	**p-value**
Age (years, mean ±SD)	56.8 (±14.7)	56.5 (±12.8)	0.940
Gender, male n (%)	19 (47.5%)	19 (51.4%)	0.736
Smoker, n (%)	6 (15.0%)	16 (45.7%)	0.004
CCI (mean ±SD)	2.93 (±2.55)	2.81 (±2.25)	0.825
Calcium blood level (mg/dL, mean ±SD)	9.57 (±0.57)	9.73 (±0.61)	0.376
Creatinine blood level (mg/dL, mean ±SD)	0.82 (±0.28)	0.90 (±0.49)	0.484
CRP blood level (mg/L, mean ±SD)	11.65 (±22.48)	6.50 (±14.22)	0.442
BMI (mean ±SD)	28.85 (±4.79)	29.05 (±5.41)	0.871
Respiratory symptoms n (%)	27 (67.5%)	16 (43.2%)	0.032
Radiological staging: Stage 1, n (%) Stage 2, n (%) Stage 3, n (%)	12 (30.0%) 25 (62.5%) 3 (7.5%)	13 (35.1%) 23 (62.2%) 1 (2.7%)	0.472
FEV1 at diagnosis (mean ±SD)	86.1 (±18.5)	85.1 (±19.9)	0.833
FVC at diagnosis (mean ±SD)	85.8 (±16.5)	83.3 (±16.5)	0.527
Size of the largest TLN (mean ±SD)	15.5 (±5.47)	16.2 (±5.44)	0.556
Location of largest LN measured on CT scan.* Mediastinal node, n (%)	33 (86.8%)	32 (88.9%)	0.788
Number of sampled lymph nodes (mean ±SD)	2.12 (±0.91)	2.22 (±0.75)	0.549
Extra nodular biopsy, n (%)	23 (57.5%)	21 (56.8%)	0.948
Positive extra nodular biopsy, n (%)	20 (87.0%)	13 (61.9%)	0.055

Abbreviations: CCI, Charlson comorbidity index. CRP, C-reactive protein. TBB, Transbronchial biopsy. EBB, Endobronchial biopsy. *TLNs are divided into several stations numbered from 1 to 14 according to lymph node location along the trachea, mediastinum, and bronchial tree. Only a few of those locations are available for biopsy by EBUS-Mediastinal nodes (2R 2L 4R 4L 7); Hilar nodes (10R 10L 11R 11L).

examined, but there were no differences between the groups.

Biopsies from other locations than TLN were taken depending on radiological findings and operator consideration (e.g. lung parenchyma biopsy by TBB or bronchial biopsy by EBB). 57.1% of subjects underwent biopsy from additional sites (i.e. non-nodal), with similar sampling rates in both groups. However, the proportion between study groups in positive granulomatous inflammation in those tissues was over 140%. The difference was marginally significant (87.0% vs 61.9% p= 0.055).

Outcomes after a one-year follow-up are presented in Table 2. The partial positive TLN group had a significantly higher rate of steroid use in the first year after diagnosis (45.0% vs. 18.9% p=0.015). The number of hospitalizations, target organ damage, and lung functions (FEV1 and FVC) were not different between the two groups a year after presentation.

For measuring covariants' influence on the main outcome, we conducted an univariable analysis for steroid treatment (presented in Table 3). We found that there was a difference in lung function at presentation between patients who were treated with

Table 2. Comparison between diffuse and partial involvement of lymph nodes. The percentage is exhibited ignoring missing data. Descriptive statistics and one-variable analysis- outcomes data.

Involvement degree	**Partial positivity N= 40 (51.9%)**	**Diffuse positivity N=37 (48.1%)**	**p-value**
Steroid treatment after a year, n (%)	18 (45.0%)	7 (18.9%)	0.015
Number of hospitalizations over a year (mean ±SD)	0.53 (±1.15)	0.27 (±0.65)	0.447
FEV1 a year after biopsy (mean ±SD)	86.5 (±17.6)	87.8 (±18.7)	0.808
FVC a year after biopsy (mean ±SD)	85.7 (±16.1)	84.0 (±15.6)	0.710
FEV1/ FVC a year after biopsy (mean ±SD)	106.8 (±8.2)	109.4 (±9.0)	0.306
Extra-pulmonary involvement *, n (%)	7 (17.5%)	8 (21.6%)	0.648
Mortality, n (%)	1 (2.5%)	1 (2.7%)	0.955

*Defined as damage to organs other than pulmonary damage (TLN and lung parenchyma)- neurosarcoidosis, cardiac sarcoidosis, dermal lesions, etc. Abbreviations: FEV1, Forced expiratory volume in one second. FVC, Forced vital capacity.

Table 3. Comparison between patients according to the requirement for steroidal treatment. Descriptive statistics and one-variable analysis. The percentage is exhibited ignoring missing data.

Steroids treatment	**No n=52 (67.5%)**	**Yes n=25 (32.5%)**	**p-value**
Age (years, mean ±SD)	55.8 (±13.8)	59.7 (±13.3)	0.143
Gender, male n (%)	26 (50.0%)	12 (48.0%)	0.869
Smoker, n (%)	17 (34.0%)	5 (20%)	0.209
CCI (mean ±SD)	2.48 (±1.99)	3.68 (±2.94)	0.044
FEV_1 at diagnosis (mean ±SD)	89.9 (±18.1)	77.2 (±18.3)	0.009
FVC at diagnosis (mean ±SD)	88.0 (±16.1)	78.0 (±15.3)	0.015
Respiratory symptoms n (%)	28 (53.8%)	15 (60.0%)	0.611
Radiological staging: Stage 1 (%) Stage 2 (%) Stage 3 (%)	18 (34.6%) 31 (59.6%) 3 (5.8%)	7 (28.0%) 17 (68.0%) 1 (4%)	0.673
Size of largest TLN (mean ±SD)	15.2 (±5.3)	17.2 (±5.6)	0.129
Location of largest LN measured on CT scan.* Mediastinal node, n	45 (90.0%)	20 (83.3%)	0.411
Extra nodular biopsy, positive n (%)	20 (66.7%)	13 (92.9%)	0.062
Diffuse positive, n (%)	30 (57.7%)	7 (28.0%)	0.015

Abbreviations: CCI, Charlson comorbidity index. C-reactive protein. TBB, Transbronchial biopsy. EBB, Endobronchial biopsy. *Mediastinal nodes (2R 2L 4R 4L 7) VS Hilar nodes (10R 10L 11R 11L).

Table 4. Comparison between diffuse and partial involvement of lymph nodes. Multivariable analysis, logistic regression for binary outcomes, and adjusted risk ratio.

	OR	95% C.I. for OR	
		Lower	Upper
FEV_1 at diagnosis	0.978	0.922	1.037
FVC at diagnosis	0.963	0.898	1.032
CCI	1.333	1.024	1.736
Diffuse positive	0.222	0.063	0.785

Abbreviations: FEV1, Forced expiratory volume in one second. FVC, Forced vital capacity.

steroids and patients who did not. The former had relatively reduced lung function (FEV1= 89.9 vs 77.2 p=0.009. FVC=88.0 vs 78.0 p=0.015) at baseline. We also noticed that people with a high comorbidities score (measured by CCI) were more likely to get treatment. Gender, age alone, smoking status, radiological staging, and lymph node characteristics (i.e., Size, location, number of sampled TLN) did not demonstrate a statistically significant effect.

A multivariable logistic regression model is presented in Table 4. We found that the adjusted odds for steroidal treatment one year after diagnosis were lower for patients with diffuse positivity TLN at presentation after controlling for comorbidity index and baseline lung function. (Adjusted OR=0.222, 95% CI 0.063-0.785; p=0.019). In this regression, CCI also demonstrates association with statistical significance (Adjusted OR=1.333, 95% CI 1.024-1.736; p=0.033).

Discussion

This study revealed that the degree of TLN involvement at presentation was associated with the need for steroid therapy. Patients with partial involvement of TLN had increased odds for oral steroidal use a year after diagnosis.

The baseline characteristics of the two groups were similar. Therefore we believe that the alteration in the degree of TLN involvement may represents an underlying trajectory that may contribute to the difference in outcome and the increased dependence on steroids.

The development of sarcoidosis requires both a genetic predisposition and environmental exposure to unknown antigens (14). The first step is an activation of the innate immunity by environmental triggers, probably airborne, followed by local phagocytosis and antigen processing by antigen-presenting cells (APCs). These cells travel to the TLN and activate T-cells by the formation of HLA-CD4 complex (15). This reaction induces a cytokine cascade resulting in further inflammatory cells migration into tissue (14).

Granuloma formation is the result of persistent antigen exposure and proinflammatory cytokine activity, especially IL-13 and TNFα, with differentiation of monocytes into epithelioid cells and T helper cells to type 1 (Th1) and type 17 helper T (Th17) cells (18). Containment of this process within the TLN is typical for stage I sarcoidosis, which in most cases goes spontaneous resolution and favorable prognosis. On the other hand, spillage of unregulated inflammation to the lung parenchyma, i.e., stage II/III sarcoidosis, is more likely to result in fibrosis, and anti-inflammatory treatment is needed in many cases (3).

Our observation, that patients with partial positive TLN were more likely to use steroids is in conjunction with this mechanism. Containment of the inflammatory process within the TLN is manifested as diffuse employment of TLN, while failure to contain the inflammatory response within the TLN, manifests as healthy-appearing TLN (or possibly undetected micro-involvement), is followed by migration of APCs and activated lymphocytes to the tissue. Similarly, patients with radiologic stage III sarcoidosis have normal appearing TLN but carry worse prognosis than stage II, sarcoidosis which has enlarged TLN (6). For some suggestions, sarcoidosis is a result of chronic inflammation caused by a failure of the immune system to remove unknown antigens. Based on that theory patients with complete TLN may represent an augmented inflammatory response compared to partial TLN disease. Failure of the inflammatory system to surge adequately and eliminate the trigger is the underlying mechanism for the persistence of the inflammatory response, the formation of granuloma in extra-lymphatic organs, and may influence the dependence on steroid treatment.

Seemingly, our hypothesis is challenged by the similar stage distribution in both groups. However, parenchymal inflammation doesn't always translate into radiological findings. It may be explained by microscopic parenchymal involvement influencing the patient's symptoms but not manifest radiologically.

Additional support for this mechanism is the increased rate of extra lymphatic disease among patients with partial positive TLN. Patients in this group had more respiratory symptoms (67.5% VS 43.2% p=0.032), and a higher rate of positive tissue biopsies (i.e. TBB or EBB) with marginal statistically significant (87.0% vs. 61.9%, p=0.055).

Both groups had similar baseline characteristics, except for smoking which was more prevalent in the diffuse positive TLN (15.0% vs. 45.7% p=0.004). The influence of smoking on sarcoidosis manifestation is controversial (19,20), with some studies suggesting a protective effect on sarcoidosis development. For this opinion, it will be reasonable to conclude that the group with higher rates of smokers will include more patients with mild disease. Smokers in our study had more TLN involvement. Nevertheless, smoking did not influence the need for treatment (34.0% VS 45.7% p= 0.209).

Several possible outcomes, including mortality, hospitalization and changes in pulmonary function were evaluated. Only the need for systemic steroids was statistically different between partial and diffuse TLN involvement. Our findings are aligned with the benign course of many patients, as well as the predictable clinical response to steroid therapy. Accordingly, dependence on immunosuppression is a reasonable marker of more aggressive disease.

In the multivariable regression model, we included age and comorbidities (CCI) since these factors have statistical significance on univariant analysis. Although pulmonary function tests were lower in the steroid group, this association disappeared in the multivariable analysis when comorbidities and age were included. This finding suggests that although poor lung function may direct the physician to begin treatment, The partial involvement of TLN has independent predictive value.

This study has several limitations: First, the retrospective nature of the study- unknown factors that were not included in our data may influence TLN involvement or clinical outcomes. Second, the relatively small number of subjects who met the inclusion criteria may precluded some variables from reaching statistical significance, and limit the number of variables we could include in our final multivariable model. However, rigorous inclusion criteria were taken to avoid misclassification bias. Last, since this was a single-center study, the histopathology may be influenced by the biopsy technique, processing, and sample interpretation. Nevertheless, our overall EBUS diagnostic yield per LN station was 76.6%. This is similar to the usual diagnostic yield, therefore we believe our results are illustrative. Genetic or local environmental factors could also affect our findings, so generalization on other locations or ethnic groups requires further exploration.

Conclusion

Our study indicates an increased risk of disease progression in patients with partial TLN involvement, imposing higher dependence on systemic steroids to reduce parenchymal loss. While we refrain from advocating treatment decisions solely based on the extent of LN involvement, we aim to shed light on a potential mechanistic pathway. We hypothesize that the absence of granuloma within the TLN signifies a failure of the immune system to contain the inflammatory process within, with migration of the inflammatory process and formation of secondary granulomas and tissue loss. To verify our observations and assess their implications on clinical management, further investigations are warranted.

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