Evaluation Of Bronchoscopic Techniques In Sarcoidosis

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***Abstract*—Aim: Sarcoidosis is a multiorgan disease characterized by the presence of non-caseified granulomas. A bronchoscopic examination is needed to make the diagnosis histopathologically. In this study, it is aimed to reveal a possible relationship between the diagnostic efficiencies of bronchoscopic examinations and the radiological extent in pulmonary sarcoidosis.**

Material and Methods: spirometry, chest X-ray and thorax computed tomography/high-resolution computed tomography, findings, presence of poor prognosis criteria, bronchoscopic technique results of 154 patients were analyzed retrospectively.

Results: The diagnostic efficiency of bronchoscopy in patients with pulmonary sarcoidosis was as high as 93.4%. Diagnostic contributions of solely transbronchial biopsy, transbronchial needle aspiration and mucosal biopsy 36.1%, 9.1% and 13.4%, respectively. The diagnostic value of transbronchial biopsy was as high in Stage 1 patients as in Stage 2 patients and was followed as the method with the highest diagnostic efficiency in all stages among all bronchoscopic methods. On the other hand, lack of a significant relationship between diagnostic efficiency of transbronchial biopsy with total radiological extent was a remarkable finding. Also, the presence of micronodular lesions around the fissure was statistically significant in patients diagnosed with sarcoidosis by mucosal biopsy. On the other hand, there was no significant relationship between the diagnostic value of transbronchial biopsy and radiological extend.

Conclusions: Considering that each of the bronchoscopic diagnostic techniques has different contributions, it was concluded that application of all three techniques in appropriate cases will increase the diagnostic effectiveness.

Keywords—Bronchoscopy, sarcoidosis, transbronchial biopsy, Transbronchial needle aspiration, Endobronchial ultrasonography

Introduction

Sarcoidosis is a systemic disease of unknown etiology characterized by the presence of non-caseified granulomas in the lungs and other organs. Chest PA displays pathological findings in lung sarcoidosis at a ratio of 85-95 % [1,2]. On the other hand, high resolution computerized tomography (HRCT) is superior compared to computerized thorax tomography (thorax BT) and other imaging methods for the assessment of parenchyma pathologies [3]. The most frequently encountered findings in thorax BT/HRCT that are in accordance with sarcoidosis are mediastinal and/or hilar lymphadenopathy, nodular opacity and micronodularities along the bronchovascular branches, ground-glass areas, pleural or subpleural nodules, nodular opacities involving air bronchogram, thickness in bronchial walls, parenchymal bands and cists, traction bronchiectasis and fibrosis [3,4]. Parenchyma involvement is mostly (50-80 %) observed symmetrically on the bilateral upper lobes. Bilateral hilar and right paratracheal lymph node (LN) expansion is observed frequently and their association is characteristic. Bilateral hilar expansion is observed in more than 95 % of the patients whereas intrathoracic lymphadenopathy (LAP) is observed in about 75 % [3,4,5].

There are several procedures for obtaining tissue for histological evaluation. Bronchoscopy; It is often done as it allows tissue sampling from various anatomical sources potentially affected by the disease, such as the airways, lung parenchyma, and hilar / mediastinal lymph nodes.

Non-caseified granuloma structure is required for the accurate diagnosis of sarcoidosis with bronchoscopy indication present in all cases [6,7]. Bronchoscopy is ranked number one among the diagnostic invasive procedures for sarcoidosis since it does not require general anesthesia, is easy to apply with high diagnostic accuracy and low complication ratio [8,9,10]. Mucosa biopsy (MB), transbronchial biopsy (TBB), LN transbronchial needle aspiration (TNA) are among the bronchoscopic methods used for sarcoidosis [11]. Although bronchoalveolar lavage fluid (BALF) is not a means of obtaining tissue for histological evaluation, it is considered a standard technique for the diagnostic examination of common parenchymal lung diseases (DPLD), including sarcoidosis. In the past decade, new endoscopic ultrasonography techniques such as endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), endoscopic ultrasound-guided fine needle aspiration (EUS-FNA), or transesophageal ultrasound-guided needle aspiration have been introduced into clinical practice by the echo bronchoscope (EUS-B-FNA). has been widely included [10]. In addition, transbronchial lung cryobiopsy (TBLC), which has been successfully used

in the diagnosis of other common parenchymal lung diseases and is a valid alternative to surgical lung biopsy in many cases, is a promising new technique that may play a role in the diagnosis of pulmonary sarcoidosis. Sarcoidosis diagnosis is made histopathologically via bronchoscopic methods as a result displaying non-caseified granulomatosis inflammation in by at least one of these methods [12]. Even though granuloma detection probability with MB is reported to vary between 40-60 %, this ratio has been indicated to reach up to 90 % by way of MB acquired from regions of mucosal irregularity, nodular appearance, edema or increase in vascularity [8,13,14]. TBB sensitivity varies between 60-90 % subject to the center it is applied on [13,14]. TNA application from LN may lead to a diagnosis rate of 63-90 %; however, biopsy application with the accompaniment of endobronchial ultrasonography (EBUS) from LN with hilar and paratracheal placement is a safer method that may increase diagnostic probability up to 91 % [10,11]. Mediastinoscopy, video-assisted transthoracic lung biopsy (VATS) or open lung biopsy may be required in cases that cannot be diagnosed despite all interventions [7,8,9]. When a general assessment is made on bronchoscopic procedures; MB is accepted as a less invasive procedure due to its easier application and the lower risk of pneumothorax involved. On the other hand; TBB is considered as a more invasive procedure due to the high risks of pneumothorax and hemorrhage involved, whereas TNA is considered as a procedure that requires experienced clinicians due to the high risks involved resulting from the proximity to largevens [8,9,10]. However, it may also be suggested to carry out all examinations together for many patients when the diagnostic efficiency of each separate method is considered for sarcoidosis [15,16].

The aim of the present study was to examine whether there is a relationship or superiority between the radiological extent and bronchoscopic examinations in order to put forth the relationship between the diagnostic efficiency of clinical and radiological findings and bronchoscopic examinations in lung sarcoidosis.

Materials and Method

The medical records of 188 patients diagnosed with histopathologically verified pulmonary sarcoidosis diagnosis during the last seven years were examined retrospectively following ethical council approval. A total of 34 cases with improper medical records or those who were not diagnosed via histopathological methods or whose pathology results cannot be obtained were excluded from the study. Results of the following examinations were taken into consideration for the 154 patients included in the study: chest PA, thorax HRCTs, spirometry, DLCO, arterial blood pressure results, biochemical examinations, presence of bad prognosis criteria and the biopsy method used in the bronchoscopic procedure.

Scoring was made by evaluating the radiological images of all patients on the histopathological diagnosis date of sarcoidosis. Chest radiographs of the patients were evaluated and radiological staging was done according to Scadding criteria. Stage 0, PA chest radiography was normal; Stage I, bilateral hilar adenopathy (paratracheal adenopathy may accompany); Stage II, parenchymal infiltration with bilateral hilar adenopathy; Stage III, parenchymal infiltration without hilar lymphadenopathy; Stage IV assessed as pulmonary fibrosis Scoring was made for thorax HRCT based on the presence and prevalence of parenchymal lesions. The parenchymal lesions were grouped as follows; ground-glass appearance, consolidation (infiltrations of larger than 10 mm), nodule (nodules with diameters ranging between 4-10 mm), micronodule (diameters ranging between 1-3 mm) (4a: Peribroncovascular area, 4b: Subpleural area, 4c: interlobular fissure neighborhoods,4d: interlobular septal areas), linear opacities (parenchymal bands, areas of linear atelectasis), interlobular septal thickening, fibrosis, bronchial lesion (bronchial wall thickening or bronchiectasis).

Lung parenchyma was separated into 6 zones. The areas above the carina level were defined as the “upper zone”, the area between the carina and inferior pulmonary vein starting levels was defined as the “central zone” while the lung area below the inferior pulmonary vein starting level was defined as the “lower zone”.

Scores were given for each lesion in each area; no lesion involvement in the zone: 0 points, less than 25 % involvement in the zone: 1 point, between 26-50 % involvement in the zone: 2 points, between 51-75 % involvement in the zone: 3 points, over 75 % involvement in the zone: 4 points. The total prevalence score for the lesion was calculated by summing up the scores obtained for each lesion from the six lung zones.

Total lung score (TLS) was calculated for each patient by summing up the lesion scores for each patient. The patients were classified into four groups based on TLS scores; Group 1 (no parenchymal involvement): TLS=0 point, Group 2 (light parenchymal involvement): TLS=1-20 points, Group 3 (moderate parenchymal involvement): TLS=21-30 points, Group 4 (severe parenchymal involvement): TAS>31 points.

BT cross-sections were also examined in addition to the parenchymal findings. The presence of LAP and their dimensions were determined based on LN stations. Right and left number 2, right and left number 4, 7 and 10-12 LN stations were evaluated separately. LNs with the largest diameter smaller than 0,5 cm were not taken into consideration as LAP. The largest diameter was recorded for each larger LN recorded as LAP. Mean dimensions were calculated for each LN stations based on LAP dimensions.

Tomography scans were evaluated together with the radiologist and the clinician.

Statistical Analysis

The data were analyzed with Statistical Package for the Social Sciences (SPSS, Inc. Chicago IL), version 22 and presented as mean ± standard deviation, number (n) and percentage (%). X2 test was used to compare categorical variables and Student T test was used to compare continuous variables. P values <0.05 were considered statistically significant.

Results

Based on the chest PA of the patients, the distribution of the radiological stages was monitored as Stage 0 9.5 %, Stage 1 48.3 %, Stage 2 29.7 %, Stage 3 10.7 %, Stage 4 1.8 % with majority of the cases at the time of diagnosis determined as stage 1. It was observed when the patients were examined with regard to the LAP distributions recorded for each LN station that the LN station number 7 (subcarinal) has the highest prevalence (91.1 %) with the largest mean size also observed in LN station number 7 with 1.93 (±0.74) cm. This was followed by LN station number 4 right with a prevalence of 87.6 % and size of 1.59 (±0.61). The highest prevalence ratio among the parenchymal findings is that of nodular opacities with 63.9 % (Figure 1).

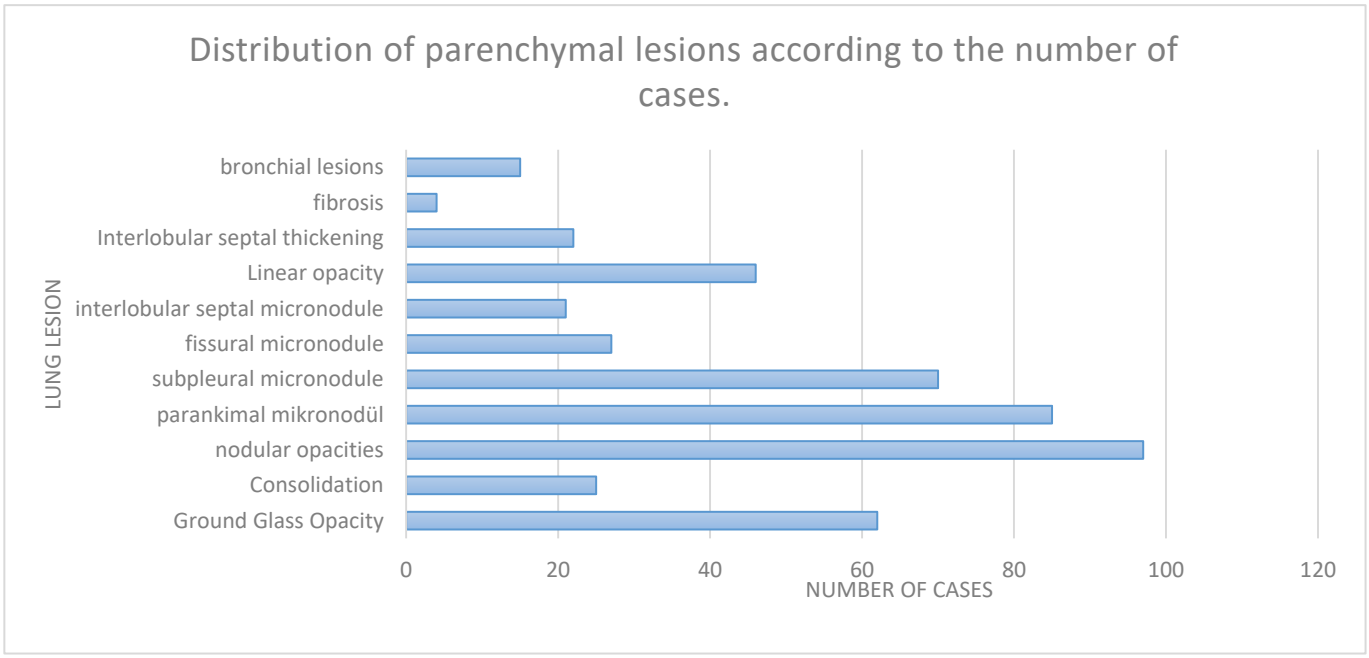

Figure 1: Distribution of parenchymal lesions by number of cases

It was observed when all micronodules were evaluated as a single group that they make up the most prevalent radiological parenchymal finding in the patients with a high ratio of 71.4 % (n=110). Figure 1 presents the distribution ratios for each radiological parenchymal finding. The mean TLS for all patients was determined as 21.13 (±13.92) based on the TLS scores with 18 cases (11.7 %) in group 1, 67 (43.5 %) cases in group 2, 43 (27.9 %) cases in group 3, 26 (16.9 %) cases in group 4 and with light parenchymal involvement in majority of the cases at the time of diagnosis.

Histopathological diagnosis was placed by at least one of the bronchoscopic diagnostic methods on 135 (87.6 % of all patients) out of a total of 146 patients subject to diagnostic bronchoscopy procedure whereas non-bronchoscopic methods were applied on the remaining 19 patients. The diagnostic efficiency of bronchoscopy was determined as 93.4 % for patients subject to bronchoscopy. MB applied on 139 (90.3 %) patients is the most frequently applied method followed by TBB. TNA applied on a total of 106 patients was observed as the least frequently used method (Table 1).

Table 1: Results of bronchoscopic diagnostic techniques

	Mucous biopsy	Transbronchial biopsy	Transbronchial aspiration
n (%)	139 (90.3%)	124 (80.5%)	106 (68.6%)
Diagnostic	52 (37.4%)	97 (78.2%)	49 (46.2%)
Non-diagnostic	87 (62.6%)	27 (21.8%)	57 (53.8%)

TBB was ranked number one with regard to both total diagnostic efficiency and by its diagnostic contribution by itself. At least one of the examination results was diagnostic in 87 out of the 90 patients subject to all three methods. This resulted in a high diagnostic efficiency of 96.6 % (Table 2).

Table 2: Diagnostic rates of bronchoscopic techniques

Bronchoscopic Techniques	Case number (n)	Diagnostic (n)	Diagnostic efficiency (%)
MB+TBB	118	112	94.9%
N-MB+TBNA	106	79	74.5%
TBB+TBNA	90	75	83.3%
MB+TBB+TBNA	90	87	96.6%

MB:Mucosal Biopsy TBB: Transbronchial Biopsy; TBNA:Transbronchial Needle Aspiration

The most frequently observed radiological stages among TBB diagnostic patients were observed as Stages 1 and 2 with equal ratios of 40.2 % (Table 3). The difference between the TBB diagnostics at these stages and other stages was observed as statistically significant ($p<0.05$). Table 3 presents a summary of the distribution of bronchoscopic diagnostic results according to radiological stages. Even though it was observed that TBB also has the highest efficiency for all stages in this assessment as well based on the ratio of the number of patients with positive results for each radiological stage to the number of patients subject to the diagnostic procedure, a statistical comparison was not made due to the distinctive differences between the number of patients in each stage (Table 3).

Table 3: Distribution of bronchoscopic diagnostic results according to radiological stages

	n	Stage 0 n %	Stage 1 n %	Stage 2 n %	Stage 3 n %	Stage 4 n %
MB diagnostic	52	2 3.8	30 57.6	16 30.7	3 5.7	1 1.9
TB diagnostic	97	6 6.1	39 40.2	39 40.2	11 11.3	3 3.0
TBNA diagnostic	49	4 8.1	15 30.6	15 30.6	-	-

MB:Mucosal Biopsy TBB: Transbronchial Biopsy; TBNA:Transbronchial Needle Aspiration

It was observed when the relationships between the LAP findings of bronchoscopic diagnostic methods for HRCT with the parenchymal findings that the LN station numbered as group 7 had the highest prevalence of TNA positive results and the largest mean size (2.02 cm±0.94). A statistically significant difference could not be determined between the mean LP sizes at the LN stations for those with positive and negative TNA ($p>0.5$).

Mean TAS was determined as 19.8 for MB positive patients from among those with diagnostic results from bronchoscopic methods, 19.8 for TBB positive patients and 23.8 for TNA positive patients. A statistically significant difference was not observed between the groups with regard to the TAS mean values.

Mucosal lesion (swelling, irregularity etc.) was observed in 33 (32 %) of the bronchoscopy patients. Reflex appearance was present corresponding to increased vascularity among the lesions in mucosal swelling, faintness, nodularity and narrow band bronchoscopic imaging. MB was taken from 60 patients without abnormal mucosal appearance in addition to the 33 patients with mucosal lesion. Positive results were obtained in 63,3 % (n=21) of the patients with mucosal lesion and 20 % (n=12) of the patients without mucosal lesion. Diagnostic efficiency of MB was observed to be quite high in patients with mucosal lesion ($p<0,05$). A statistically significant relationship could not be determined between the mucosal lesions and MB diagnostics and the clinical and radiological weights. Even though a statistically significant correlation could not be determined between MB diagnostics and TAS, the micronodules around the fissure were observed to be high at a statistically significant level in the MB positive group ($p<0,01$).

Scores for each parenchymal lesion pattern and TBB positivity ratios for TLS were compared in order to determine whether there is a correlation between the parenchyma involvement pattern and prevalence. A statistically significant relationship could not be determined between the diagnostic value of TBB and TLS. While the parenchymal pattern with the highest mean score among TBB positive cases was the peribroncovascular micronodules, the nodules were negative. Statistically significant scores were observed for subpleural micronodules in the diagnostic group and for nodule and interlobulerseptal thickening in the non-diagnostic group ($p<0,05$). These results were considered to be significant with regard to the fact that the diagnostic efficiency of TBB is not related with radiological extent in the parenchyma.

Discussion

MB is a simpler, less invasive method with a lower complication rate compared to TBB and TNA with a considerably high diagnostic efficiency. Different results have been put forth in various studies between the diagnostic value of MB and mucosal lesion presence. In addition to studies indicating that the presence of abnormal findings in the mucosa does not eliminate the need for MB, there are also various studies in which the diagnostic efficiency of MB acquired from abnormal mucosae was observed to be considerably high [17,18,19]. Even though it was determined based on our results that there is a statistically significant correlation between mucosal lesion presence and MB positivity, the detection of 20 % positivity in those without mucosal lesion can be interpreted as an indication that MB is a procedure

that should be applied on suitable patients even when no mucosal lesion is observed. In addition to publications indicating that there is no statistically significant relationship between the radiological stage of the disease determined based on chest PA and the diagnostic value of MB, there are also studies which put forth higher diagnostic values for patients in Stage 1 and 2 compared to those of patients in Stage 3 [18,19,20]. Stage 1 is the most frequently observed stage among the MB positive patients with 57,1 % whereas stages with the highest diagnostic value were Stage 1 and 2. The fact that in accordance with literature, MB positivity was lower in our patients in Stages 3 and 4 compared with Stages 1 and 2 can be explained by the involvement of mediastinal LAPs observed in Stages 1 and 2 together with the involvement of submucosal lymphatics.

It has been reported in studies on the diagnostic value of TBB that it may vary between 40 % to 90 % [22-26]. In the present study, we observed the diagnostic value of TBB for our patients as 78,3 % which is a high value and determined that it has the highest diagnostic value among the diagnostic methods. Even though TBB is considered as having a higher complication risk among the bronchoscopic methods, the ratio of pneumothorax development is about 5-7 % and that of major hemorrhage is lower than 1 % [17,25]. These risks are at acceptable ratios when the high diagnostic value of TBB is taken into consideration. It is indicated as a result of studies on TBB that diagnostic value increases with increasing stage of the disease, increasing parenchyma involvement, having a sufficient number of biopsies (about four-six) and acquiring TBB from more than one lobe [27,29]. It has been reported in studies on the diagnostic value of TBB with radiological stages that the diagnostic values of TBB vary between 55-60 % in Stage 1 and about 75 % in Stage 2 [30]. While Stages 1 and 2 are among the most frequently encountered radiological stages among our TBB diagnostic patients with equal ratios of 40 % (total 80 %) with diagnostic value of Stage 1 cases not less than those of Stage 2 patients. Boer et al. carried out a study in which diagnostic value of TBB was associated with ground glass lesions and the prevalence of reticular patterns; asserting that nodules do not have superiority with regard to the diagnostic value of TBB even though they are observed more frequently due to the fact that their distributions are patchy [27]. According to our results, there was no statistically significant correlation between the diagnostic value of TBB and TLS. However, it was determined when the scores for each lesion were examined separately that the peribroncovascular micronodules have the highest score in the diagnostic group, while nodules have the highest score in the non-diagnostic group.

There are various studies in related literature on the increase of diagnostic value following the inclusion of TNA with TBB during the diagnostic bronchoscopic procedure for sarcoidosis. Morales et al. carried out a study in which diagnosis ratios increased from 60 % to 83 % in Stage 1 cases with the inclusion of TNA with TBB while it increased from 76 % to 86 % in Stage 2 cases 11. Whereas it was reported in the study by Trisolini et al. that the diagnostic value increased from 41 % to 88 % for Stage 1 and from 79 % to 90 % for Stage 2 [31]. While the general diagnostic value ratio in our study which was 78,3 % with was TBB increased up to 84,3 % with the inclusion of TNA. It is indicated that diagnostic value increases for the diagnostic bronchoscopy procedure for sarcoidosis by the inclusion of MB and TNA to TBB [32,33]. According to the study by Torrington et al., diagnostic value increased by 14 % with the inclusion of MB to TBB (18). The same increase was reported by Halme et al. as 8 % [33]. The increase in diagnostic value with the inclusion of MB to TBB was observed in our study as 16,6 %. Diagnostic value increase for the joint use of TBB and TNA was reported by Morales et al. as 10-23 % and by Leonard et al. as 23 % [11,25]. In accordance with previous literature, we observed in our study that the diagnostic value of TBB increased by 5,03 % with the inclusion of TNA and by 18,3 % when all three procedures were carried out.

TNA still holds an important place in our day among the bronchoscopic diagnostic methods for sarcoidosis. It has become a very advantageous method compared to an invasive procedure such as mediastinoscopy due to the fact that it can be applied to outpatients and that it enables acquiring samples from the hilar lymph nodes in addition to the mediastinal lymph glands [34,35,36]. On the other hand, its diagnostic value depends on the experience of the cytologist since the biopsy material acquired is not as large as that in mediastinoscopy. It has been reported in studies related with the diagnostic value of TNA that the diagnostic values were determined to be higher for biopsies carried out in the accompaniment of endobronchial ultrasonography (EBUS) which was reported to vary between 60,9-90,3 % in different studies [37-42]. The diagnostic value of TNA was determined to be slightly lower (46,4 %) compared with the current literature. This can be explained by the fact that the TNA procedure was not carried out in the accompaniment of EBUS for all patients and that each case was not evaluated by a cytopathologist expert in this field. Studies on the relationship between the diagnostic value of TNA and radiological stages which report that the diagnostic value is higher in Stage 1 compared with Stage 2 have put forth a hypothesis that the acquired result can be explained by the greater granuloma loads of LNs in Stage 1 [31,32]. In accordance with the literature findings, our study results also indicate that diagnostic value is higher for Stage 1 and 2 patients.

Conclusion

The diagnostic value of bronchoscopy was observed at a high value of 91,8 % in our study carried out on patients subject to bronchoscopy. Taking into consideration the contribution of each diagnostic bronchoscopic procedure on the diagnosis,

it can be stated that applying all three procedures on as much patients as possible will increase the diagnostic value. On the other hand; the fact that contrary to the general clinical approach, the diagnostic value of TBB was observed as high in Stage 1 cases as those of Stage 2 cases can be explained by the fact that TBB is the procedure with the highest diagnostic value in all stages, that there is a statistically significant relationship between the diagnostic values of TAS and TBB despite the fact that the highest values have been observed in the TBB positive group among the mean TAS values and the fact that TBB holds an indispensable spot for cases subject to bronchoscopy with sarcoidosis pre-diagnosis. In addition; we are of the opinion that the diagnostic value of MB is considerably high for Stage 1 and 2 patients with higher submucosal lymphatic involvement which should be kept in mind as a striking point.

The fact that the study is retrospective, that the diagnostic bronchoscopy procedures have been carried out by different doctors and that the biopsies taken were evaluated by many different pathologists at different times are the limitations of our study. The results can be improved by carrying out more comprehensive and multi-centered prospective studies.

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