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INTERVENTIONAL BRONCHOSCOPY

Utility of Bronchoalveolar Lavage and Transbronchial Biopsy in Patients with Hypersensitivity Pneumonitis

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Abstract

Introduction Making the diagnosis of HP is challenging due to a lack of consensus criteria and variability of both pathologic and radiographic findings. The purpose of this retrospective study was to determine the diagnostic utility of the combination of BAL lymphocyte count and TBBX in patients with HP.

Methods We conducted a retrospective cohort study of all patients with a MDD diagnosis of HP at a single center.

Results 155 patients were included in the study. 49% of patients who underwent BAL had a lymphocyte count > 20, 42% had a lymphocyte count > 30, and 34% had lymphocyte count > 40%. The median BAL lymphocyte count was higher in inflammatory HP compared to fibrotic HP. The addition of TBBX to BAL significantly increased the diagnostic yield regardless of the BAL lymphocyte cutoff used. The yield of bronchoscopy with TBBX and BAL when a lymphocyte count > 40% was used as a cutoff was 52%.

Conclusions Our study suggests that the combination of TBBX with BAL significantly increases the likelihood that the procedure will provide adequate additional information to allow a confident MDD diagnosis of HP and may reduce the need for SLB in the diagnostic workup of HP.

Introduction

Hypersensitivity pneumonitis (HP) is a group of granulomatous, interstitial, bronchiolar, and alveolar-filling pulmonary diseases caused by repeated exposure and sensitization to a variety of antigens [1]. HP is an increasingly recognized cause of interstitial lung disease (ILD) [2, 3]. HP was traditionally thought to occur in acute, subacute, and chronic forms [4, 5]; however, because this classification is not associated with survival or treatment response, recent literature has moved toward classification of HP patients as inflammatory or fibrotic, with inflammatory patients having better survival [6–11].

It is important to diagnose HP accurately because its prognosis and treatment are distinct from other forms of ILD, including idiopathic pulmonary fibrosis (IPF) [12–14]. However, making the diagnosis of HP remains challenging due to variability of clinical findings and lack of consensus criteria [15–17]. A history of exposure has been shown to be the most powerful determinant of an HP diagnosis, which requires a thoughtful approach that may span multiple patient encounters [18, 19]. Unfortunately an exposure is not always found in patients with HP [11]. High resolution computed tomography (HRCT) features in HP can be highly variable. Patterns range from wide spread air-trapping without fibrosis to usual interstitial pneumonia (UIP) pattern with extensive honeycombing [20, 21]. A prior study showed that the absence of a lower zone predominance, centrilobular nodules and significant mosaic attenuation can help distinguish HP from IPF and nonspecific interstitial pneumonia (NSIP) [20]. However, it is unclear how many of these features needed to be present to reach a confident diagnosis of HP [20, 22].

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In patients with both an exposure history and a suggestive HRCT, the need for additional invasive testing remains unclear. Two recent papers reached different conclusion in this regard [15, 23]. However, in patients without a clearly identifiable fibrogenic antigen or an HRCT that is nondiagnostic, additional invasive testing is required [24]. HP is classically associated with lymphocytic predominant bronchoalveolar lavage [25], but prior studies show a wide range of lymphocyte counts in patients with HP [15, 26], which may be related to the degree of fibrosis [10]. Transbronchial biopsy (TBBx) can be diagnostic in certain forms of ILD, such as granulomatous lung disease [27]. While tissue obtained from TBBx may be inadequate or nondiagnostic [19, 28, 29], TBBx can be performed at the same time as the BAL and has the potential to confer additive information regarding diagnosis with only minimal increase in risk [30, 31].

The purpose of this retrospective study is to examine the diagnostic workup of a large cohort of HP patients from a single center and to determine the diagnostic utility of combining BAL lymphocyte count and TBBx for patients with suspected HP. We hypothesize that bronchoscopy will be a useful diagnostic adjunct for this disease and that adding TBBx to BAL will significantly increase the likelihood that bronchoscopy will provide adequate information to allow a multidisciplinary diagnosis (MDD) of HP.

Methods

The study cohort included patients that were retrospectively identified in the Advanced Lung Disease Clinic at University of Texas Southwestern Medical Center (UTSW). The UTSW Institutional Review Board approved the study (STU 022017-006). Patients with a known, or suspected, diagnosis of HP underwent MDD for the purposes of this study, similar to prior studies [32]. Patients were excluded if they did not have a MDD of HP.

Clinical data extracted from the medical record included age, gender, smoking history, causative antigen, results of pulmonary function testing (PFTs), BAL lymphocyte percentage, TBBx results, Surgical Lung Biopsy (SLB) results, response to exposure removal, date of death, and date of lung transplantation. A thoracic radiologist evaluated each HRCT [12]. We used a pre-specified combination of HRCT features to categorize each HRCT based on prior report, which included the presence of upper/mid lung predominance, centrilobular nodules, and mosaicism in ≥ 3 lobes [20]. Using these criteria, we defined a HRCT as "likely HP" if 2 or 3 of 3 features were present, "possible HP" if 1 of 3 features was present, and "unlikely HP" if 0 of 3 features was present.

Patients were classified as inflammatory if they had no fibrosis on HRCT and as fibrotic if they had any fibrosis [9, 10]. Because the BAL lymphocyte percentage that is considered suggestive of HP varies in the literature, we analyzed BAL lymphocyte percentages of 20, 30, and 40% separately [10, 15, 19, 23]. TBBx was considered characteristic of HP if it had granulomas, particularly loose granulomas or giant cells and at least one of the following: inflammatory bronchiolitis or a predominantly mononuclear cellular interstitial infiltrate [9, 33, 34].

Statistical Analysis

Continuous variables were expressed as means and standard deviations; comparisons were made using Student's t test or Wilcoxon signed rank sum test as appropriate. Categorical variables were expressed using counts and percentages; comparisons were made using χ^2 test or Fisher's exact test, where appropriate. The proportion of patients with HP and BAL lymphocyte count above each cutpoint (>20, >30, or $>40\%$) alone were compared to the number of patients with BAL lymphocyte count above the same cutpoints or TBBx with features suggestive of HP using chi-squared test. All p values < 0.05 were considered significant. Statistical analyses were performed using R version 3.3.2 statistical analysis software (http://www.R-project.org).

Results

Patient Characteristics

Demographic characteristics of the retrospective cohort are shown in Table 1. Mean age was 61.9 years, and 80% of the patients were non-Hispanic white. There was no gender skew in our cohort. A sensitizing antigen was found in 89% of the cohort; 64% of patients had an avian antigen identified, while 40% had mold. Among those with avian antigen exposure, there was no difference between those with bird versus feather products (Supplemental Table 1). At baseline, this cohort had moderate impairment in lung function. Eighty-eight percent of patients had either a TBBx or SLB performed in the diagnostic evaluation. The median follow-up time was 3 years, during which 13% of the cohort died and another 12% required lung transplantation. The median time from diagnosis to death or transplant was 12.7 years.

Bronchoscopy Results

Of the 77 patients who underwent bronchoscopy, 53 (68.8%) had a BAL and 72 (93.5%) had a TBBx (Table 2). Of the 78 patients who did not have a bronchoscopy, 48 had a surgical biopsy prior to referral to our center, and 8 were considered too sick to tolerate the procedure (Supplemental Table 2). Forty-nine percent of patients with BAL had lymphocyte

Table 1 Demographic characteristics of patients with hypersensitivity pneumonitis

	Hypersensitivity pneumonitis ($n=155$)
Mean age (SD)	61.9 (10.8)
Male, no. (%)	78 (51)
Ethnicity, no. (%)	
Non-Hispanic White	126 (80)
Black	3 (2)
Hispanic or Latino	10 (6)
Asian	5 (3)
Other	1 (1)
Unknown	10 (6)
Ever smoker, *N* (%)	75 (48)
Pack years, median (IQR)	19 (7–37)
Antigen identified, no. (%)	138 (89)
Bird	55 (35)
Feather	44 (28)
Any avian	99 (64)
Mold	62 (40)
Any avian and mold	31 (20)
Other	14 (9)
Unknown	17 (11)
Baseline lung function, mean (SD), *N*	
FVC % predicted	69 (19), 104
FEV1% predicted	71 (19), 104
FEV1/FVC ratio	80 (9), 104
DLCO % predicted	54 (19), 97
HRCT available for scoring	154 (99)
Lung biopsy performed[a]	133 (86)
Surgical biopsy	92 (59)
Transbronchial biopsy	72 (47)

[a]Some patients had both transbronchial and surgical lung biopsy

count > 20, 42% had lymphocyte count > 30, and 34% had lymphocyte count > 40%. The median BAL lymphocyte count was higher in inflammatory (46, 20–80) compared to fibrotic HP (19, 11–41, $p=0.009$) (Supplemental Table 3).

TBBx was characteristic of HP in 29 of 72 patients (40.2%) who had TBBx performed. Among the 26 patients with < 20% lymphocytes on BAL who underwent TBBx, TBBx was characteristic of HP in 12 patients (46.2%). There was no difference between inflammatory and fibrotic patients in the overall yield of TBBx. TBBx revealed granulomas or giant cells in 41.7%, inflammatory bronchiolitis in 17.7%, and interstitial inflammation in 59.7% (Supplemental Table 3). The addition of TBBx significantly increased the yield of the procedure regardless of the BAL lymphocyte cutoff used (Table 2). Even if the most stringent BAL lymphocyte percentage was used (> 40%), the combination of BAL and TBBx had a yield of 52%.

Table 2 Comparison of bronchaolveolar lavage to bronchoalveolar lavage or transbronchial biopsy in the diagnosis of hypersensitivity pneumonitis (overall $N=77$, inflammatory $N=17$, fibrotic $N=60$)

	BAL alone[a]	BAL or TBBx[b]	*p* value
BAL 20% cutoff			
Overall	26 (34)	45 (58)	**0.004**
Inflammatory	10 (59)	13 (76)	0.46
Fibrotic	16 (27)	32 (53)	**0.005**
BAL 30% cutoff			
Overall	21 (27)	41 (53)	**0.002**
Inflammatory	9 (53)	12 (71)	0.48
Fibrotic	12 (20)	29 (48)	**0.002**
BAL 40% cutoff			
Overall	18 (23)	40 (52)	**0.0005**
Inflammatory	8 (47)	11 (65)	0.49
Fibrotic	10 (17)	29 (48)	**0.0005**

Bold values indicate statistical significance ($p<0.05$)

[a]Bronchoalveolar lavage suggestive of hypersensitivity if lymphocyte count above cutpoints (20, 30, or 40%, respectively)

[b]Bronchoalveolar lavage lymphocyte count (> 20, 30, or 40%, respectively) or transbronchial biopsy feature suggestive of hypersensitivity pneumonitis (granulomas, giant cells, inflammatory bronchiolitis, cellular interstitial infiltrate)

Additional Diagnostic Testing

HRCT Findings

Ninety-nine percent of patients in the cohort underwent HRCT during their diagnostic evaluation (Table 3). Thirty percent of the scans were classified as likely HP, 41% as possible and 29% as unlikely. Eighty-six percent of our cohort had fibrosis, and 90% of patients had an HRCT that was inconsistent with UIP. The most common inconsistent features included extensive ground glass (57%), mosaic attenuation in ≥ 3 lobes (51%), peribronchovascular predominance (42%), and mid/upper lung predominance (36%).

MDD

The MDD discussion is difficult to codify due to the large number of potential data combinations. However, when we examined the individual data points that contributed to a final MDD of HP (Table 4) several things were clear. The HRCT was considered likely HP in only 30%. The two most important data points for this diagnosis were the identification of an exposure and consistent findings on pathology. Each of those was present in over 85% of the cases. BAL lymphocyte percentage was independently valuable in only 17%. Fifteen of the 18 patients who did not have pathology demonstrated significant objective improvement with removal of the exposure.

Table 3 HRCT findings for hypersensitivity patients ($n=154$)

HRCT features	Hypersensitivity pneumonitis ($n=154$)
HRCT pattern, *N* (%)	
Definite UIP	10 (7)
Possible UIP	6 (4)
Inconsistent with UIP	138 (90)
Extent of fibrosis, *N* (%)	
None	22 (14)
Mild (< 10%)	43 (28)
Moderate (10–50%)	60 (39)
Severe (> 50%)	29 (19)
HRCT reticulation, *N* (%)	131 (85)
HRCT traction bronchiectasis, *N* (%)	123 (80)
HRCT honeycombing, *N* (%)	53 (34)
Inconsistent with UIP features, *N* (%)	
Mid/upper lung predominant fibrosis	55 (36)
Peribronchovascular predominance	65 (42)
Extensive ground glass > reticulations	88 (57)
Centrilobular nodules, no. (%)	29 (19)
Mosaic attenuation in ≥ 3 lobes	77 (51)
Cysts, no. (%)	13 (8)
Consolidation, no. (%)	16 (10)
Probability of HP based on HRCT, *N* (%)[a]	
Unlikely HP (0/3 features)	45 (29)
Possible HP (1/3 features)	64 (41)
Likely HP (2–3/3 features)	46 (30)

[a]HP HRCT features include air trapping, mid/upper lung predominance, and centrilobular nodules [20]

Table 4 Description of variables that contributed to multidisciplinary diagnosis of hypersensitivity pneumonitis

Individual clinical features[a]	Number with feature, (%) ($N=155$)
Exposure identified	138 (89)
Response to removal of exposure	15 (10)
HRCT findings	46 (30)
BAL lymph > 20	26 (17)
Pathologic findings	137 (88)

[a]Individual patients may fit in more than one category

Discussion

Role of Bronchoscopy

In this study, we examined the role of bronchoscopy in a well-defined cohort of MDD-defined HP cases. We defined the yield of bronchoscopy as the additional data obtained allowed a confident MDD diagnosis of HP. The yield of BAL alone was 23–34% in our cohort depending on the BAL lymphocyte percentage cutoff used, and the mean BAL lymphocyte percentage in fibrotic HP was only 19%. This confirms prior reports that BAL lymphocyte percentage is normal in a large percentage of fibrotic HP [19, 35, 36].

Further, our study demonstrates that the yield significantly increases to 52–58% with the addition of TBBx to BAL even though a strict pathologic definition that included a requirement for granulomas or giant cells plus either inflammatory bronchiolitis or a cellular interstitial infiltrate was used [9, 33, 34]. Prior studies have demonstrated characteristic findings of HP in only 11–25% of TBBx [19, 28, 29]. In contrast to prior studies, TBBx was characteristic of HP in 40.2% of all patients in our study who underwent TBBx and in 46.2% of patients who had < 20% BAL lymphocytes. There was no difference between inflammatory and fibrotic patients in the yield of TBBx. The reason for the higher yield off TBBx seen in this study is unclear but may be due to our cohort, which included only MDD-confirmed cases of HP as opposed to all cases of suspected HP. This has important implications in that a surgical biopsy can be avoided in approximately half of patients who are eventually diagnosed with HP.

Patient Characteristics

Our demographic data is similar to that of prior published cohorts. In 3 prior studies, mean age ranged from 53 to 60, and 37–53% of patients were male. The percentage of current and former smokers ranged from 42 to 51% [11, 22, 37]. In one study, median survival was 18.2 years among those with an identified antigen and 9.3 years among those without an identified antigen [22]. This is consistent with our median time from diagnosis to death or transplant of 12.7 years.

Antigen identification in prior cohorts is variable, ranging from 42.9 to 75%, likely reflecting the difference in inclusion criteria between studies and whether the presence of feathers alone without bird exposure was considered a sensitizing antigen [11, 22, 37]. Our study reveals a higher antigen detection rate than the reported literature, likely because we included patients with just a feather antigen and did not require SLB for inclusion in the study. Our results demonstrate that patients with feather exposure have similar diagnostic study results compared to those with bird exposure suggesting that feather exposure is a sensitizing antigen even in the absence of direct bird exposure.

A prior study of HRCT findings reported reticulation in 100% of HP patients, air trapping in 75%, centrilobular nodules in 56%, upper lung zone predominance in 11%, and random zonal predominance in 58% [20]. Our results differ from that study in that fewer patients in our cohort

had reticulations and centrilobular nodules, though the prior study required SLB for inclusion. Most prior studies have not attempted to codify what percentage of HRCTs in HP patients are considered likely HP versus possible HP by a thoracic radiologist. In our cohort, HP was considered likely HP in only 30% and possible HP in an additional 41%. Only 27% of the patients had both a likely HP CT and an identified exposure while 8% had neither. The implication is that additional testing will be required in the majority of patients.

Limitations

There are several limitations to this study. Potential for bias exists because all patients were from a single academic center. To limit incorporation bias, we utilized MDD, which is the current gold standard for the diagnosis of ILD. We had significant objective data on which to base our MDD; 88% of patients in our cohort had pathologic evidence of HP, while 10% had an objective response to exposure removal. Our pathologic definition of a characteristic TBBx was also strict, including a requirement for granulomas or giant cells plus an additional feature of the classic HP triad.

Given the retrospective design, BAL and TBBx were not performed for all patients in the study, and selection bias may exist. We cannot exclude confounding variables that may make BAL or TBBx results more likely to be diagnostic. Finally, we do not have a control group of patients who underwent bronchoscopy in the diagnostic workup of ILD who were subsequently given diagnoses other than HP so we were unable to assess sensitivity and specificity of bronchoscopy.

Conclusion

The results of our study suggest that bronchoscopy is a useful tool in the evaluation of patients who are ultimately diagnosed with HP. Our study shows that combining TBBx with BAL significantly increases the likelihood that the procedure will provide adequate additional information to allow a confident MDD diagnosis of hypersensitivity pneumonitis. BAL and TBBX may reduce the need for SLB in the diagnostic workup of HP.

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Compliance with Ethical Standards

Conflict of interest The authors have no conflicts of interest to report.

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