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LETTER TO THE EDITOR

Role of Antigen Type in Survival in Chronic Hypersensitivity Pneumonitis

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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, the most common of which are avian and mold exposure [1]. Prior studies report conflicting results with regard to the effect of antigen type on survival in HP [2–4]. To evaluate whether history of avian or mold exposure is associated with clinical outcomes, we evaluated a retrospective cohort of patients with a multidisciplinary diagnosis of HP for an association between avian or mold exposure and overall and transplant-free survival. We also evaluated the diagnostic yield of bronchoscopy in these patients in order to assess for lead-time bias as a possible confounder.

We conducted a retrospective cohort study of all patients with a MDD diagnosis of HP at a single center between 2007 and 2017 as previously described [1]. We identified antigen exposure through a detailed history. We defined inflammatory HP as the absence of fibrosis on HRCT. We defined a characteristic BAL as a lymphocyte percentage greater than 20 and a characteristic TBBx as granulomas or giant cells and either an inflammatory bronchiolitis or a predominantly mononuclear cellular interstitial infiltrate [1]. Continuous variables were expressed as means and standard deviations and comparisons were made using Student's *t* test. Categorical variables were expressed using counts and percentages; comparisons were made using Chi-squared test or Fisher's exact test, where appropriate. The primary outcome of this study was overall survival for patients with mold or avian exposure, defined as time from diagnosis of interstitial lung disease to death with censoring at time of transplant. A secondary analysis of transplant-free survival, where transplant is equivalent to death, was performed to assess the handling of the transplant event. The association between exposure type and overall survival and transplant-free survival were assessed using univariable and multivariable Cox proportional hazards regression. Known predictors of survival, including age, gender, baseline forced vital capacity (FVC) percent predicted and diffusion capacity of lung for carbon monoxide (DLCO), were included in a multivariable model.

The demographic and radiographic characteristics of our retrospective cohort of 155 patients with a multidisciplinary diagnosis of HP has been previously reported [1]. Of these 155 patients, 31 (20.0%) had only mold exposure and 68 (43.9%) had only avian exposure. Thirteen patients (13.1%) died during the study period, and 14 (14.1%) underwent lung transplantation. The antigen type was not associated with overall survival (HR 0.51, 95% CI 0.15–1.48, $p=0.22$) or transplant-free survival (HR 0.74, 95% CI 0.34–1.60, $p=0.44$) in a univariable model. In a multivariable model adjusted for gender, FVC % predicted, or DLCO % predicted, antigen type was not associated with overall survival (HR 0.56, 95% CI 0.17–1.86, $p=0.35$) or transplant-free survival (HR 0.95, 95% CI 0.40–2.25, $p=0.91$).

There was no difference in the number of patients with inflammatory HP between groups (6.5% and 16.2%, $p=0.22$, for mold and avian exposure, respectively) (Table 1). There was no difference in the number of patients with a diagnostic BAL or a characteristic TBBx between those with mold exposure compared to those with avian exposure (44.4% vs 50.0%, $p=0.77$, for BAL and 45.5% vs 46.9%, $p=0.92$, for TBBx). There was no difference in the median lymphocyte percentage between groups (33, IQR 0–68, vs 27, IQR 7–46, $p=0.51$). The overall yield of bronchoscopy, defined as either a diagnostic BAL or a characteristic TBBx, was not different between the groups (64.3% vs 68.8%, $p=0.79$).

Our findings help to resolve conflicting data in the literature with regard to the effect of the type of antigen on mortality in HP. A prior study of patients with HP diagnosed by surgical lung biopsy (SLB) suggested that patients with avian antigen exposure have a better survival than patients

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Table 1 Diagnostic test characteristics of patients with avian compared with mold antigen exposure

	Mold antigen $N=31$	Avian antigen $N=68$	p-Value
Inflammatory, N (%)[a]	2 (6.5)	11 (16.2)	0.22
Fibrotic, N (%)[b]	29 (93.5)	57 (83.8)	
BAL lymph > 20, N (%)	4/9 (44.4)	11/22 (50)	0.77
Median lymphocyte percentage, IQR	33, 0–68	27,7–46	0.51
TBBx characteristic, N (%)[c]	5/11 (45.5)	15/32 (46.9)	0.92
Characteristic either TBBx or BAL, N (%)[d]	9/14 64.3	22/32 (68.8)	0.79

[a]Inflammatory patients were defined as having no fibrosis on HRCT

[b]Fibrotic patients were defined as having mild, moderate, or severe fibrosis on HRCT

[c]TBBX was characteristic of HP if granulomas or giant cells and either inflammatory bronchiolitis changes or interstitial inflammation was present

[d]BAL was characteristic of HP if > 20% lymphocytes were present

with other antigen exposures [2]. Another study of HP patients diagnosed with SLB demonstrated that the type of antigen did not affect mortality in a multivariable model [4]. Finally, a study of HP patients at the Mayo Clinic, which required histopathologic evidence of HP only if an antigen was not identified, revealed that patients with avian antigen exposure were more likely to have fibrosis on HRCT than those without avian antigen, but this did not correspond to a change in mortality [3].

Our study adds to the literature by including an evaluation of the diagnostic workup. This finding helps to eliminate lead-time bias, as patients with a diagnostic bronchoscopy may be diagnosed sooner than those who require SLB which could affect outcomes. Further, our study population more closely approximates HP patients seen in tertiary academic centers because we included patients with a multidisciplinary diagnosis of HP, which is the current gold standard for diagnosis. The aforementioned articles have either been stringent in requiring SLB for inclusion or had a lenient case definition. While the small sample size and low event rate limits our power to detect a difference in overall survival, our study is the largest in the literature to address the association between antigen type and survival. Our results demonstrate that the type of antigen is not associated with survival, yield of bronchoscopy, or presence of fibrosis on HRCT.

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Compliance with Ethical Standards

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

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