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Diagnostic implications of positive avian serology in suspected hypersensitivity pneumonitis

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ABSTRACT

Background: The diagnostic evaluation of patients with interstitial lung disease (ILD) often involves serologic assessment for identifiable causes such as hypersensitivity pneumonitis (HP). While not on its own defining of HP, precipitin serologies are often obtained to support clinical suspicion if other findings are inconclusive. We studied the clinical relevance of positive avian serology in patients undergoing ILD evaluation.

Material and methods: We identified individuals with positive avian serology (>53.3 mg/L) and undifferentiated ILD seen at our institution over a three-year period. Clinical, laboratory, pathologic, and radiologic findings were evaluated for consensus HP diagnosis by two expert pulmonologists, blinded to presenting serology levels.

Results: Ninety-one ILD subjects with positive avian serology were identified; mean age was 62.7 ± 15.3 years with a slight male predominance (56%). Forty-nine (54%) received a consensus HP diagnosis. Those with HP had higher mean avian serology titer (95.0 ± 38.7 mg/L vs. 68.3 ± 16.7, ($P < 0.0001$). Never-smokers also had higher titers compared to prior or active smokers ($P = 0.0008$). Positive avian protein exposure ($P < 0.0001$, OR 21.3 (6.4–87)), DLCO% ($P = 0.04$, unit OR 0.96 (0.92–0.99)), and increasing serology titer ($P < 0.015$, unit OR 1.03 [1.01–1.06]) were independent predictors of HP diagnosis.

Conclusion: Among patients with positive avian serology, those with higher titers were more likely to have HP diagnosis. Nonsmokers also manifested higher titers compared to those with smoking history. These results may guide the usage and interpretation of avian serology screening in the initial assessment of suspected HP.

1. Introduction

The diagnostic evaluation of patients with interstitial lung disease (ILD) often involves clinical assessment and serologic testing for identifiable causes such as hypersensitivity pneumonitis (HP). Although no consensus criteria exist, HP diagnosis often includes history of exposure to a potential inciting antigen, supportive findings on lung imaging, and positive precipitin serology consistent with prior exposure and antigen sensitization [1–3].

Despite suggestive features, the utility of serology in patients with suspected HP or uncharacterized ILD remains inconclusive. Confident diagnosis appears to be weighted more by exposure history, representative computed tomography (CT) findings, and pathologic features if lung biopsy is pursued than serology findings, though they are still often obtained when the above findings are dubious or inconclusive. Whether positive serology should sway a clinician towards supporting HP diagnosis if other supportive clinical features are equivocal is unknown. The purpose of this study was to review the diagnostic utility of positive avian serology in patients undergoing ILD workup.

2. Material and methods

IRB approval was obtained (IRB #13–007760). All patients with ILD seen at Mayo Clinic, Rochester, between 2009 and 2012 with elevated avian serology ("Pigeon Breeder's Disease Serology" in the Mayo Medical Laboratories, Rochester, MN) were included in the study. Positive avian serology was defined as a precipitin titer greater than 53.3 mg/L. Presenting demographic and clinical data were reviewed and abstracted, including respiratory symptoms,

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Abbreviations

CT	chest computed tomography
DL_{CO}	diffusing capacity for carbon monoxide
FEV_1	forced expiratory volume in the first second
FVC	forced vital capacity
HP	hypersensitivity pneumonitis
HRCT	high-resolution computed tomography
ILD	interstitial lung disease
PFT	pulmonary function testing

exposure to birds or feather containing products, smoker status (ever vs never), pulmonary function testing (PFT), chest computed tomography (CT), bronchoalveolar lavage (BAL) with cell differential for lymphocytosis, and histopathology, if obtained. Collated PFT studies included percent predicted forced expiratory volume in the first second (FEV1%), forced vital capacity (FVC%), and diffusion capacity for carbon monoxide (DLCO%) at presentation. Chest CT interpretations were reviewed and classified as either suggestive or supportive of typical HP findings (upper and mid lung zone predominance, poorly defined centrilobular micronodules or ground glass opacities, mosaic attenuation suggestive of air-trapping [so called 'head cheese' appearance], and fibrosis with no or minimal honeycombing) vs other CT patterns characteristic of other interstitial lung disease [4,5]. Histopathology where obtained (surgical and transbronchial biopsies) was categorized as either supportive of HP as interpreted by the original reading pathologist, or considered non-specific or inconsistent.

Final consensus HP diagnosis was determined by two expert pulmonologists (TM and JHR) based on the following criteria: the presence of all three of the following clinical characteristics: 1) respiratory symptoms, 2) radiologic evidence of diffuse lung disease, and 3) no other identifiable cause for lung disease; in addition to at least one of the following: (a) lung biopsy with features of HP, (b) bronchoalveolar lavage (BAL) lymphocytosis >15%, or(c) high-resolution (HRCT) findings suggestive of HP. As positive exposure history may be suggestive of HP but obtained variably based on patient recall and clinician solicitation, we did not include it as part of disease diagnosis but studied it as a predictive parameter. HP disease subtypes included chronic, subacute, and acute, defined by the duration of presenting symptoms and radiologically by the following: presence of any reticulation or fibrosis as 'chronic', the absence of fibrosis but with predominant diffuse and lobar ground glass and mosaic attenuation as 'subacute', and diffuse centrilobular ground glass or micronodularity without other features as 'acute'. Non-HP diagnoses were classified in the following manner: idiopathic pulmonary fibrosis (IPF) based on standard criteria, connective-tissue disease related interstitial lung disease (CTD-ILD) based on the presence of rheumatologist-defined autoimmune disease, other idiopathic interstitial pneumonia (based on pathology or suggestive radiologic findings), and sarcoid. Additional non-HP categories included unclassifiable ILD defined by clinical and radiologic presentation not meeting IPF criteria but having no other secondary etiology or cause, and non-ILD where presentation and radiologic findings were suggestive of another clinical process (infection, heart failure, or aspiration). Frequency and degree of avian precipitin titer elevation in patients with HP diagnosis were compared to other presenting features of disease including positive exposure history and typical radiologic or histologic findings.

2.1. Statistical analysis

Continuous data were presented as mean ± standard deviation (SD) with range, while categorical data were presented as counts and percentages. Comparisons with Kruskal-Wallis or Chi square and ANOVA were performed based on data type. Univariable and multivariable logistic regressions were performed for predictors of HP diagnosis, correcting for a priori covariables of exposure history, FVC%, and DLCO%. CT and pathology findings were not used as clinical predictors as they were part of the study consensus disease definition. Two-tailed P values < 0.05 were considered statistically significant.

3. Results

A total of 91 consecutive patients being assessed for ILD were found to have positive avian serology (mean serology titer 82.7 ± 33.2, 53.4–197). Associated demographics are presented in Table 1. Of these, 49 (54%) received a consensus diagnosis of HP. Mean age at ILD presentation was 62.7 ± 15.3 years with a slight male predominance (56%). Positive exposure history was described in 60% of patients, with approximately half of subjects (N = 45) undergoing either transbronchial or surgical lung biopsy. The most common presenting PFT pattern was restriction (59%), followed by normal (13%) and obstruction (12%).

Final disease diagnoses after study review are presented in Table 2. Chronic HP was the dominant HP subtype (69%) followed by subacute (10%). Among final non-HP diagnoses, unclassifiable ILD (39%) and other IIP (26%) were most common.

Frequencies of positive diagnostic findings associated with HP are presented in Table 3. Of 51 individual biopsies obtained, only 10 (19.6%, 8 surgical and 2 transbronchial) demonstrated histopathologic features consistent with HP. CT findings consistent with HP were found in less than half of patients (47%), along with BAL lymphocytosis >15% (39%).

Comparison of clinical findings in those with consensus HP vs non-HP is presented in Table 4. All patients had respiratory symptoms at the time of presentation though dyspnea was more prevalent in those with HP vs. non-HP (98% vs 82%, P = 0.02). Eighty-nine patients had chest CT with 42 (47%) demonstrating findings suggestive of HP. Of this cohort, 40 (95%) received a final HP consensus diagnosis. Cell count and differential was performed in 18 of 29 BAL (62%) with no difference in frequency of lymphocytosis between consensus HP and non-HP (P = 0.15). All patients with consistent pathology findings received a final consensus HP diagnosis. Patients with consensus HP also had greater exposure history (85% vs 31%, P < 0.0001) and lower FVC% (58.8 vs 69.6, P = 0.006) and DLCO% (45.9 vs 79.6, P = 0.03) at presentation.

Stratification of the cohort by presence of avian protein exposure history is presented in Table 5. Those with positive exposure history smoked less (35% vs 60%, P = 0.02), had more suggestive CT findings of HP (57% vs 35% P = 0.04), BAL lymphocytosis (6 vs 1, P = 0.03) and higher pigeon breeder serology (92.1 ± 38.5 vs 71.7 ± 21.4, P = 0.003). The majority had consensus diagnosis of HP (36 vs 13 cases, P < 0.0001), while of note, 27% of those with positive exposure were not ultimately diagnosed with HP.

Results of positive avian serology are presented in Table 6. Those with consensus HP diagnoses had a mean avian serology titer of 95.0 ± 38.7 mg/L (53.4–197.0), compared to 68.3 ± 16.7 (54.3–124.0) in non-HP, (P < 0.001). Frequency of positive consensus diagnoses as stratified by serology cut-offs was also statistically significant (P = 0.02).

Univariable and multivariable predictors of HP diagnosis are presented in Table 7). Increasing serology titer was associated with HP diagnosis (unit OR 1.03 (1.01–1.06), P < 0.0153) even after