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Utility of anti-neutrophil cytoplasmic antibody screening in idiopathic interstitial lung disease

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Abstract. Background: Interstitial lung disease (ILD) is an established manifestation of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis. Autoimmune serologic screening is recommended by international consensus guidelines during the evaluation of idiopathic ILD, but ANCA testing only on a case-by-case basis. **Objective:** We aimed to evaluate the role of ANCA screening in patients with idiopathic ILD. *Methods:* We performed a retrospective review of patients seen between September 2015 and April 2017 in the ILD clinic at Toronto General Hospital. Patients referred with confirmed or suspected connective tissue disease were excluded. Patient demographics, symptoms, chest imaging, and pulmonary function testing was collected. We performed descriptive statistics based on the presence of ANCAs and estimated operating characteristics for ANCA screening. **Results:** In total, 360 patients with idiopathic ILD were reviewed, 159 met study inclusion criteria and 4 (2.5%) tested positive for ANCAs. Two patients (1.2%) had elevated myeloperoxidase-ANCAs (MPO-ANCA) and 2 (1.2%) had elevated proteinase-3-ANCAs (PR3-ANCA). There were no significant associations between patient demographics and ANCAs. One patient (0.6%) with PR3-ANCAs was diagnosed with vasculitis following rheumatologic evaluation. Despite negative ANCA testing, 1 patient (0.6%) was diagnosed with vasculitis following rheumatologic evaluation. The sensitivity and specificity of ANCA screening for vasculitis in patients with ILD was calculated as 50% (95% CI, 1.3%-98.7%) and 98% (95%CI, 4.4-155.5) respectively. Negative and positive likelihood ratios were 0.5 (95%CI 0.1-2.0) and 26.2 (95%CI 4.4-155.5) respectively. **Conclusion:** ANCA screening in patients with idiopathic ILD rarely yields positive results. These results support an individualized approach to ANCA testing as opposed to widespread screening.

Key words: Interstitial lung disease, vasculitis, screening

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides encompass a group of systemic inflammatory syndromes, characterized by necrotizing inflammation of the small blood vessels (1). Three distinct vasculitides with varied clinical manifestations exist: microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA), and granulomatosis with polyangiitis (GPA). ANCAs are seen in >90% of GPA, >70% of MPA and ~40% of EGPA

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(2-4). Myeloperoxidase antibodies (MPO-ANCA), and proteinase-3 antibodies (PR3-ANCA) comprise the ANCA antibodies, and have varying sensitivities and specificities for the diagnosis of each vasculitis (5).

Interstitial lung disease (ILD) is a heterogeneous group of diffuse parenchymal lung diseases associated with significant morbidity and mortality. Autoimmune disease has been recognized as a common cause of ILD, implicated in approximately one-third of patients presenting to subspecialty ILD clinics (6). Of the ANCA-associated vasculitides, ILD occurs most commonly in MPA, recognized in approximately 7% of patients (7). Computed tomography (CT) chest imaging in patients with vasculitis-ILD often demonstrates honeycombing, with some meeting criteria for a usual interstitial pneumonia (UIP) pattern, a pattern most commonly seen with idiopathic pulmonary fibrosis (IPF) (8,9). Clinicians must maintain a high index of suspicion for inflammatory conditions, including vasculitis, when evaluating patients with idiopathic ILD. Experts overwhelmingly agree that autoimmune serological testing should be performed during the evaluation of idiopathic ILD; current international guidelines recommend antinuclear antibodies (ANA), rheumatoid factor (RF) and cyclic-citrullinated (CCP) antibodies be sent in all patients with idiopathic ILD (10). The value of screening for vasculitis using ANCAs in patients with idiopathic ILD is still debated. Identifying systemic vasculitis in patients presenting with idiopathic ILD may prevent the need for a surgical lung biopsy and influence therapeutic decisions. Our aim was to evaluate the utility of ANCA screening in patients with idiopathic ILD.

Methods

Study population

We performed a retrospective review of consecutive patients seen in the ILD clinic at Toronto General Hospital referred with idiopathic ILD. Respirologists and Rheumatologist with expertise in ILD staff the clinic. Participants were over 18 years of age and seen between September 2015 and April 2017. Patients were excluded from the study if there was confirmed or suspected connective tissue disease (CTD) at the time of referral, no evidence of ILD, did not undergo complete antibody testing, or were not seen by an ILD expert universally screening for ANCA. Confirmed or suspected CTD was determined by a review of the patient's medical history at the first evaluation and the reason for referral in the consultation note or referral request. The diagnosis of vasculitis was based on the reported clinical impression of the treating ILD Respirologist and Rheumatologist. Institutional research ethics board approval was obtained and the research performed in accordance with the Declaration of Helsinki.

Clinical data and serology

Patient age, gender, CTD symptoms (arthritis, gastroesophageal reflux, rashes, sicca symptoms, sclerodactyly, myositis), computed tomography (CT) imaging pattern, smoking status, and pulmonary function testing (PFT) [forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLCO)] data was collected. Symptoms of CTD were based on patient reports as documented in the clinical notes. A standardized questionnaire is used as part of the initial evaluation for all new patients in the ILD clinic, ensuring the screening of CTD symptoms. All CT imaging was reviewed by a thoracic radiologist and classified in accordance to international guidelines. All patients evaluated for idiopathic ILD had a panel of antibodies performed for screening purposes, which included ANA, RF, CCP, myositis antibodies and ANCA. Testing was performed at the Toronto General Hospital in accordance with local laboratory practices. Both MPO-ANCA and PR3-ANCA testing were performed using a Bioplex enzyme-linked immunosorbant assay (ELISA). Abnormal ANCA levels are considered above 0.2 AI units.

Statistical analysis

Descriptive statistics were performed based on the presence of ANCAs. Univariate analysis using the Chi-squared (or Fishers exact test where appropriate) and student's t-test or Wilcoxon rank sum tests were performed. The level of statistical significance was set as p-value<0.05. Statistical analyses were performed using SAS University Edition (Cary, North Carolina, USA).

Results

Three hundred and sixty patients with idiopathic ILD were reviewed. The impact of ANCA screening

was evaluated in 159 (44.2%) (Tab. 1). Subjects were excluded due to: (1) suspected or confirmed CTD at time of referral [91 patients (45.3%)]; (2) absence of ILD [19 patients (9.5%)]; (3) patients were not seen by a pulmonologist involved in the study [65 patients (32.3%)] and (4) complete serologic testing was not performed at the first opportunity [26 patients (12.9%)].

Of the 159 patients with idiopathic ILD, 4 patients (2.5%) tested positive for ANCAs. There were no significant differences in patient demographics based on ANCA screening results (Table 2). Two patients were found to have p-ANCA (MPO-ANCA) and two patients c-ANCA (PR3-ANCA). Only 1 (0.6%) patient with elevated ANCA levels was diagnosed with vasculitis after a rheumatologic evaluation; this patient was noted to have a rash in the lower extremities and subungual splinter hemorrhages on examination. Of the patients screening positive for ANCA, the patient with vasculitis had the highest level (PR3-ANCA 6.5 AI units). The three subjects with elevated ANCA levels without vasculitis were deemed to have idiopathic pulmonary fibrosis (IPF), idiopathic non-specific interstitial pneumonia (NSIP) and undifferentiated-CTD respectively. One patient was prescribed antifibrotic therapy, one immunosuppression (prednisone and azathioprine) and one did not require any treatment. No patients with ANCAs were found to have an inconsistent with UIP CT imaging pattern. A summary of the clinical characteristics of patients with positive ANCAs are highlighted in Table 3. Despite negative ANCA testing, 1 patient (0.6%) with idiopathic ILD was diagnosed with vasculitis by a rheumatologist and was treated with immunosuppression following a thorough evaluation.

Operating characteristics of ANCA screening for detecting vasculitis-ILD were estimated using a contingency table (Figure 1). The sensitivity and specificity of ANCA screening for vasculitis-ILD was calculated as 50.0% (95% CI, 1.3%-98.7%) and 98% (95% CI, 94.5%-99.6%) respectively. The resulting negative and positive likelihood ratios were 0.5 (95%CI, 0.13-2.04) and 26.2 (95%CI, 4.4-155.5) respectively. Given vasculitis-ILD is a rare disease (estimated as 10-20 cases per 100,000) the positive and negative predictive values were estimated as 0.0% and 100.0% respectively (11). The negative and positive predictive values do not significantly change if you consider the estimated prevalence of vasculitis in patients with IPF (estimated as 0.6%) (12). The false positive rate was 1.8%. Two of three cases with false positive ANCAs were MPO-ANCA.

Based on an estimated cost per test of $70.00, a total of $11,130 dollars was spent on ANCA testing during the study period.

Table 1. Characteristics of patients seen in an ILD clinic for idiopathic ILD.

	ILD patients (n=159)
Age § (years)	69.5 (14.5)
Gender, n(%)	
Male	96 (60.4)
Female	63 (39.6)
FVC – % predicted §	71.0 (26.0)
DLCO – % predicted ‡	72.6 (20.5)
CTD symptoms	77 (48.4)
CT pattern	
UIP	44 (27.7)
Possible UIP	68 (42.8)
Inconsistent UIP	46 (28.9)
Smoking status	
Never	63 (39.4)
Current	12 (7.5)
Ex-smoker	84 (52.5)
Raynauds phenomenon	10 (6.3)
Inflammatory Arthritis	8 (5.0)
GER	43 (27.0)
Rash	15 (9.4)
Sicca	17 (10.7)
Sclerodactyly	3 (1.9)
Myositis	6 (3.8)
Lung biopsy	32 (20.1)
Antifibrotics treatment	46 (28.9)
Corticosteroid treatment	56 (35.2)
Oxygen treatment	36 (22.6)
ANCA	4 (2.5)
ANA positive	31 (19.5)
RF positive	21 (13.2)
CCP positive	5 (3.1)

‡ Represents normally distributed continuous variables with the mean ± SD and interquartile range calculations, (Shapiro-Wilk >0.05); § Represents non-normally distributed continuous variables with the median and interquartile range calculations; ANA, antinuclear antibodies; ANCA, anti-neutrophil cytoplasmic antibodies; RF, rheumatoid factor; CCP, anti-cyclic citrullinated peptide; CTD, connective tissue disease; CT, computed tomography; FVC, forced vital capacity; DLCO, diffusing capacity of the lung for carbon monoxide; GER, gastroesophageal reflux.

Table 2. Characteristics of patients seen with idiopathic ILD stratified by the results of screening ANCA testing.

	ANCA- ILD (n=155)	ANCA+ ILD (n=4)	P-Value
Age § (years)	69.0 (15.0)	74.0 (16.0)	0.27
Gender, n(%)			
Male	94 (60.7)	2 (50.0)	0.65
Female	61 (39.4)	2 (50.0)	
FVC – % predicted §	71.0 (26.0)	73.0 (49.0)	0.87
DLCO – % predicted ‡	73.0 (20.6)	59.0 (5.1)	0.18
CT pattern			
UIP	43 (27.7)	1 (25.0)	0.40
Possible UIP	65 (41.9)	3 (75.0)	
Inconsistent UIP	46 (29.7)	0 (0.0)	
Smoking status			
Never	63 (40.7)	0 (0.0)	0.21
Current	12 (7.7)	0 (0.0)	
Ex-smoker	79 (51.0)	4 (100.0)	
Raynauds phenomenon	10 (6.5)	0 (0.0)	>0.99
Inflammatory Arthritis	8 (5.2)	0 (0.0)	>0.99
GER	41 (26.5)	2 (50.0)	0.36
Rash	14 (9.0)	1 (25.0)	0.27
Sicca	17 (11.0)	0 (0.0)	>0.99
Sclerodactyly	3 (1.9)	0 (0.0)	>0.99
Myositis	6 (3.9)	0 (3.8)	>0.99
Lung biopsy	31 (20.1)	1 (25.0)	>0.99
Antifibrotics treatment	45 (28.9)	1 (25.0)	>0.99
Corticosteroid treatment	54 (34.8)	2 (50.0)	0.61
Oxygen treatment	34 (21.9)	2 (50.0)	0.22
ANA positive	31 (19.5)	0 (0.0)	>0.99
RF positive	21 (13.6)	0 (0.0)	>0.99
CCP positive	5 (3.2)	0 (0.0)	>0.99

‡ Represents normally distributed continuous variables with the mean ± SD and interquartile range calculations, (Shapiro-Wilk >0.05); § Represents non-normally distributed continuous variables with the median and interquartile range calculations; ANA, antinuclear antibodies; ANCA, anti-neutrophil cytoplasmic antibodies; RF, rheumatoid factor; CCP, anti-cyclic citrullinated peptide; CTD, connective tissue disease; CT, computed tomography; FVC, forced vital capacity; DLCO, diffusing capacity of the lung for carbon monoxide; GER, gastroesophageal reflux.

Discussion

We found universal screening for ANCAs in patients with idiopathic ILD rarely yields positive results and had little influence on disease treatment. Only one patient with ANCAs was diagnosed with vasculitis-ILD in our cohort, and the presence of additional clinical features in that case would likely have prompted ANCA testing independent of a widespread screening study. These results support an individualized approach to ANCA testing, and provide some evidence for avoiding the inclusion of ANCAs in serologic screening panels when evaluating idiopathic ILD.

The ANCA-associated vasculitides comprise a rare group of diseases, with an estimated incidence of 10-20 cases per million individuals (12). Interstitial lung disease is reported to occur in a subset of patients with vasculitis, roughly 3% of all patients and up to 7% of patients with MPA (7). Although ILD has become an increasingly recognized pulmonary complication of vasculitis, it remains a relatively uncommon manifestation of a rare disease. We found ANCA positivity to be infrequent and vasculitis-ILD to represent ~1% of patients referred with idiopathic ILD. The lower frequency of ANCA in our ILD cohort compared some other reports may be due to differences in study ethnicity; previous studies have found MPO-ANCAs to be more prevalent among Asian populations (13,14). We suspect the Canadian population is more ethnically diverse. The prevalence of ANCA seropositivity and vasculitis-ILD in our cohort are similar to that reported by Liu et al., who found 4% of IPF patients to have ANCAs and approximately 0.7% of IPF patients to develop vasculitis in an American cohort (15).

The 2018 clinical practice guidelines for idiopathic pulmonary fibrosis do not recommend universal ANCA screening based on expert opinion (10). However, some investigators have suggested screening for ANCA in patients with idiopathic ILD is reasonable, given ILD can be the first manifestation of vasculitis and a delay in diagnosis may impact patient care (16,17). We aimed to estimate operating characteristics for ANCA screening in patients with idiopathic ILD, but did not restrict our cohort to patients with IPF, as has been the case with other research (15). The World Health Organization has published extensively on the characteristics of an ideal screening test, suggesting that screening tests be highly sensitive to limit missed cases (18). We estimated the sensitivity of ANCA screening for vasculitis-ILD to be 50%, a threshold that is suspected to be too low to justify universal testing. ILD is a more common manifestation of MPA, and ANCA testing has a lower sensitivity for MPA than GPA (2,15). This in part may limit the utility of ANCA screening in those presenting with ILD as a primary disease feature.

Although the negative predictive value was

Table 3. Clinical summaries of patients with positive anti-neutrophil cytoplasmic antibodies and ILD.

Age/Sex	ANCA (titre)	CTD symptoms	Other Positive Serology (Y/N)	CT Pattern	Lung Biopsy (Y/N)	Referring Dx	Final Dx	Treatment
80F	p-ANCA (6.0 AI units)	None	N	UIP	N	ILD NYD	IPF	Antifibrotics
66M	c-ANCA (1.1 AI units)	GER	N	Possible UIP	Y	iNSIP	iNSIP	Steroid/AZA
68M	c-ANCA (6.5 AI units)	Splinter hemorrhages, rash, GER	Jo-1	Possible UIP	N	ILD NYD	vasculitis-ILD	Steroid/AZA
86F	p-ANCA (2.3 AI units)	None	SRP	Possible UIP	N	ILD NYD	uCTD-ILD	None

p-ANCA, anti-neutrophil cytoplasmic antibodies against myeloperoxidase; AZA, azathioprine; CT, computed tomography; CTD; connective tissue disease; uCTD, undifferentiated connective tissue disease; Dx, diagnosis; GER. Gastroesophageal reflux; ILD, interstitial lung disease; iNSIP, idiopathic non-specific interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; NYD, not yet diagnosed; SRP, signal recognition peptide antibodies; UIP, usual interstitial pneumonia.

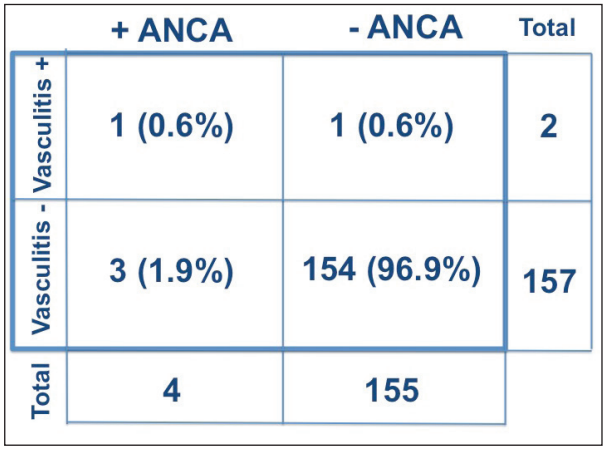

Figure 1. Contingency table for the frequencies of anti-neutrophil cytoplasmic antibodies and vasculitis in patients evaluated for idiopathic interstitial lung disease.

calculated as 100%, this is influenced by disease prevalence, and vasculitis is a rare condition. The frequency of vasculitis-ILD did not change irrespective of whether ANCA results were positive or negative (0.6% vs. 0.6%). Mandl et al. reported the test characteristics for ANCAs in patients who underwent testing for any purpose (19). They found that when ANCA testing is performed in a heterogenous, real-world population, it had poor diagnostic accuracy. Limiting ANCA testing to cases with at least one guideline-based criteria for vasculitis identified 100% of cases, supporting previously published criteria for ANCA testing. Interstitial lung disease is not a guideline-based indication for ANCA testing; the pulmonary indications being pulmonary haemorrhage, nodules, and large airway stenosis (20).

The implications of ANCAs in ILD patients without evidence of systemic vasculitis are evolving. Kagiyama et al. identified ANCAs in up to 7% of patients with IPF, but the development of vasculitis in only 0.5% (21). This suggests that the majority of positive ANCA results in patients with IPF fail to alter the clinical diagnosis. In a large cohort of IPF patients, Liu et al. found no association between ANCA status and disease severity or transplant-free survival (15). ANCAs are not included in the definition for interstitial pneumonia with autoimmune features (IPAF), a heterogeneous group with suspected inflammatory lung disease based in clinical, serologic and morphologic criteria (22). These patients are often treated with immunosuppressive therapy, despite not meeting formal criteria for CTD (23). As a result, the presence of isolated ANCAs in the absence of other features of vasculitis are unlikely to impact treatment, prognosis or research classification.

Several limitations of this research need to be highlighted. Firstly, although ANCA were systematically performed for all patients with idiopathic ILD, the retrospective study design is susceptible to selection bias. We excluded patients referred with suspected CTD as these patients were likely to have pre-existing symptoms that would prompt serologic testing. Secondly, cases were reviewed over a two-year period, but we did not systematically repeat ANCA testing on subsequent visits, and were therefore unable to evaluate for ANCAs seroconversion or clinical features of vasculitis over time. Thirdly, we did not systematically document the presence of other conditions associated with ANCAs, such as inflammatory bowel disease and malignancy. However, patients were reviewed carefully as part of their clini-

cal care, with rheumatologist involvement. Fourthly, our institution performs ANCA testing by ELISA assays, whereas other facilities may use alternative methods for ANCA detection, such as indirect immunofluorescence (IIF). However, ELISA assays for ANCAs are commonly employed around the world, and are currently the recommended screening test according to international consensus guidelines (24).

The prevalence of ANCAs in patients with idiopathic ILD is low when applying a systematic screening approach. Limiting ANCA testing to patients with symptoms of CTD would have reduced costs and likely identified a similar number of vasculitis-ILD cases. These results support a thorough clinical evaluation for vasculitis when assessing patients with idiopathic ILD, but a personalized approach to individualized ANCA testing.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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