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INTERSTITIAL LUNG DISEASE

Screening for Myositis Antibodies in Idiopathic Interstitial Lung Disease

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Abstract

Purpose International guidelines recommend screening for connective tissue disease (CTD) with autoantibodies when evaluating patients with idiopathic interstitial lung disease (ILD). Idiopathic inflammatory myositis comprises of a subgroup of CTD diagnosed with myositis antibodies (MA), often presenting with ILD. Our aim was to evaluate the utility of MA screening in patients with idiopathic ILD.

Methods A retrospective analysis was conducted on patients referred with idiopathic ILD to a tertiary centre ILD clinic who were screened for MA. Patients with known or suspected CTD were excluded. Descriptive statistics, univariate analysis and multivariable logistic regression were used to detect associations between MA and patient characteristics.

Results Of 360 patients, 165 met inclusion criteria and 44 (26.7%) were identified to have MA. Fourteen patients (8.5%) had a change in diagnosis as a result of MA screening. Multivariable logistic regression identified the presence of MA to be associated with current smoking [OR 6.87 (1.65–28.64), $p=0.008$] and a diffusing capacity of $<70\%$ predicted [OR 2.55 (1.09–5.97), $p=0.03$]. In patients with a change in diagnosis due to MA screening, 3 (1.8%) underwent a surgical lung biopsy and 2 (1.2%) were previously treated with antifibrotic therapy.

Conclusions Screening for MA in patients with idiopathic ILD can contribute to a change in patient diagnosis, and may prevent invasive testing and unproven use of antifibrotic therapy. These results support the addition of MA to CTD screening panels during the initial evaluation of idiopathic ILD.

Keywords Connective tissue disease · Idiopathic inflammatory myositis · Interstitial lung disease

Abbreviations

ANA	Antinuclear antibodies
ARS	Aminoacyl-tRNA synthetase antibodies
aSS	Antisynthetase syndrome
antiCCP	Anti-cyclic citrullinated peptide
CT	Computed tomography
CTD	Connective tissue disease
DLCO	Diffusing capacity of the lung for carbon monoxide
FVC	Forced vital capacity
GER	Gastroesophageal reflux
IIM	Idiopathic inflammatory myositis
ILD	Interstitial lung disease
IPF	Idiopathic pulmonary fibrosis
MAA	Myositis-associated antibodies
MA	Myositis antibodies
MSA	Myositis-specific antibodies
NSIP	Non-specific interstitial pneumonia
PFT	Pulmonary function testing
RF	Rheumatoid factor
SLB	Surgical lung biopsy
SRP	Anti-signal recognition particle
UIP	Usual interstitial pneumonia

Notation of Prior Abstract Publication/Presentation A poster of preliminary data was presented at a local University of Toronto Respirology Research Day.

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Introduction

Connective tissue disease (CTD) is a common cause of interstitial lung disease (ILD) being diagnosed in approximately 15% of patients presenting with idiopathic ILD [1]. In 2011, international consensus guidelines recommended screening for CTD during the evaluation of idiopathic ILD with antinuclear antibodies (ANA), rheumatoid factor (RF) and anti-cyclic citrullinated peptide (antiCCP) antibodies [2]. These diagnostic guidelines were updated in 2018 and acknowledge routine testing for myositis antibodies, but conclude these antibodies be performed on a case-by-case basis [3].

Idiopathic inflammatory myopathies (IIM) are a heterogeneous group of CTD, characterised by inflammation of skeletal muscles. Nearly 50% of IIM patients develop ILD, with even higher rates occurring in the antisynthetase syndrome (aSS) a subgroup of IIM characterised by ILD, myositis, Raynaud's phenomenon, fever and mechanics hands [4–6]. Antibodies in IIM are often categorised as myositis-associated antibodies (MAA) or myositis-specific antibodies (MSA). Myositis-associated antibodies are seen in myositis overlap syndromes, whereas MSA are associated with IIM, and include aminoacyl-tRNA synthetase antibodies (ARS), which are associated with the aSS [6]. Collectively, MAA and MSA will be referred to as myositis antibodies (MA) in this article.

Distinguishing CTD-ILD from other idiopathic ILD is critical. Immunosuppressive medications are the mainstay of treatment for CTD-ILD, but are associated with increased mortality in patients with idiopathic pulmonary fibrosis (IPF) [4]. Screening for IIM in idiopathic ILD led to a new diagnosis in 6.6% of patients in a Japanese cohort, suggesting that screening may enhance diagnostic accuracy [5]. However, studies screening for IIM have included patients with undifferentiated CTD (uCTD) and excluded drug-related and occupational ILD [5]. Our aim was to (1) evaluate the diagnostic utility of MA screening in patients with idiopathic ILD and (2) evaluate for predictors of MA positivity.

Materials and Methods

Study Population

A retrospective review of adult patients (≥ 18 years) referred for idiopathic ILD to the ILD clinic at Toronto General Hospital was conducted. The clinic is staffed by pulmonologists with expertise in ILD. Data were collected between September 2015 and April 2017. Exclusion criteria included confirmed or suspected CTD at the time of referral, absence of ILD, MA testing not performed at the first opportunity, or not being seen by an ILD expert. Patients with suspected CTD after being assessed in the ILD clinic were referred to a rheumatologist for evaluation. The diagnosis of a CTD was based on the clinical assessment performed by the treating physicians (rheumatologist/ILD pulmonologist). We recorded the treating physicians' clinical diagnosis at the time of referral, after first assessment by an ILD physician and after the performance of MA testing. Myositis antibody screening was deemed to result in a change of diagnosis if the final diagnosis as provided by the treating ILD pulmonologist and/or rheumatologist was directly altered by the MA panel results.

Clinical Data

Patient age, gender, CTD symptoms (arthritis, gastroesophageal reflux, rashes, sicca symptoms, sclerodactyly, myositis), computed tomography (CT) imaging pattern, smoking status and pulmonary function testing [forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLCO)] were collected. All CT imaging were reviewed by a thoracic radiologist and classified in accordance to international guidelines [2].

Myositis Antibody Testing

All patients evaluated for idiopathic ILD underwent screening for MA at the Mitogen Advanced Diagnostics Laboratory (Calgary, Alberta) with the Euroimmun AG (Lubeck, Germany), Euroline Autoimmune Inflammatory Myopathies 16 Ag immunoblot. The antibody panel consisted of MAA [nuclear matrix protein-2 (NXP2), anti-RNA degrading complex (PM/Scl-75, PM/Scl-100), anti-DNA nuclear binding protein (Ku), anti-E3 ligase (Ro-52)] and MSA [Jo-1 (anti-histidyl), EJ (anti-glycyl), OJ (anti-isoleucyl), PL-7 (anti-threonyl), PL-12 (anti-alanyl)], anti-nucleosome remodelling complex (Mi-2, Mi-2α, Mi-2β), transcriptional intermediary factor 1-gamma (TIF1) melanoma differentiation-associated gene 5 (MDA5) and anti-signal recognition particle (SRP) antibodies.

Statistical Analysis

Descriptive statistics were performed based on the presence of MA and whether MA testing led to a change in clinical diagnosis. Univariate analysis using the Chi-squared (or Fishers exact test where appropriate) and student's *t* test or Wilcoxon rank-sum tests was performed. Multivariable logistic regression was used to evaluate for associations between patient characteristics and the presence of MA.

Variable selection was performed using a backward selection strategy, retaining only variables with p value of ≤ 0.2 in the model. The global null hypothesis was evaluated using the Omnibus likelihood ratio, with a level of significance set as p value < 0.05. The model fit was evaluated using the Hosmer–Lemeshow test. Statistical analyses were performed using SAS University Edition (Cary, North Carolina, USA).

Results

Three hundred and sixty patients with idiopathic ILD underwent screening for MA as part of their diagnostic evaluation. Of these, 165 patients met criteria for study inclusion. Subjects were excluded as a result of suspected or confirmed CTD at time of referral in 91 (46.7%); absence of ILD in 19 (11.5%); MA not being sent at the first opportunity in 20 (12.1%); not being seen by an ILD expert involved in the study in 65 (33.3%).

The most common reasons for referral were ILD of unclear cause (48.2%) and suspected IPF (35.1%). In patients with a change in diagnosis after a clinical evaluation, the most common revised diagnoses were CTD-ILD [20 patients (12.1%)] and IPF [40 patients (24.2%)].

In total, 44 of 165 (26.7%) patients with idiopathic ILD were found to have MA (Table 1). The most common MA was Ro-52 identified in 18 (10.9%) subjects. Of the MSA, Jo-1 (5 (3.0%)) and PL-7 (5 (3.0%)) were the most common. The presence of multiple MA in the same individual was seen in 12 (7.3%) patients, with 9 (5.5%) patients having two antibodies and 3 (1.8%) patients having three antibodies.

Patient characteristics at the time of screening were stratified by the presence of MA (Table 2). Current smoking status, DLCO and CT imaging pattern were associated with the presence of MA in univariate analysis (Table 2). In patients with MA, other antibody results (ANA, RF and antiCCP antibodies) were negative in 27 (61.4%). No association was identified between the referring diagnosis and presence of MA ($p = 0.62$). The referring diagnoses in patients with MA were ILD of unclear cause (50.0%), IPF (36.4%), cryptogenic organising pneumonia (6.8%), unclassifiable ILD (4.5%) and eosinophilic pneumonia (2.3%). A multivariable regression model found current smoking [OR 6.87 (1.65–28.64), $p = 0.008$] and DLCO < 70% predicted [OR 2.55 (1.09–5.97), $p = 0.03$] to be associated with increased odds of MA positivity upon screening (Hosmer–Lemeshow test, $p = 0.08$, c statistic = 0.73) (Table 3).

Overall, 14 (8.5%) patients experienced a change in diagnosis as a result of MA screening ($p < 0.0001$). The resulting diagnoses in patients that experienced a change due to MA screening included 6 (42.9%) with aSS, 3 (21.4%) with other IIM, 2 (14.2%) with undifferentiated CTD, 1 (7.1%) with scleroderma/myositis overlap, 1 (7.1%) with interstitial pneumonia with autoimmune features, and 1 (7.1%) with unclassifiable ILD.

Table 1 Frequency of myositis antibodies identified as a result of screening patients with idiopathic interstitial lung disease

Myositis antibodies	*n* (%)
Any antibody	44 (26.7)
Ro-52	18 (10.9)
PM/Scl75	8 (4.8)
Jo-1	5 (3.0)
PL-7	5 (3.0)
PL-12	4 (2.4)
PM/Scl100	4 (2.4)
SRP	4 (2.4)
Ku	3 (1.8)
MDA-5	2 (1.2)
Mi-2β	2 (1.2)
TIF-1γ	2 (1.2)
NXP2	1 (0.6)
EJ	1 (0.6)
Mi-2α	1 (0.6)
Mi-2	0 (0.0)
OJ	0 (0.0)
Combination antibody	12 (7.3)
Jo-1/Ro-52	2 (1.2)
PL-12/Ro-52	2 (1.2)
Ku/Ro-52	1(0.6)
EJ/Ro-52	1 (0.6)
SRP/PM/Scl75	1 (0.6)
SRP/Mi-2β	1 (0.6)
PM/Scl75/PM/Scl100	1 (0.6)
SRP/Mi-2α/PM/Scl75	1 (0.6)
PM/Scl75/PM/Scl100/Ro-52	1 (0.6)
Jo-1/PM/Scl75/Ro-52	1 (0.6)

Patient characteristics were stratified by whether MA screening led to a change in patient diagnosis (Table 4). A change in diagnosis as a result of MA screening occurred more in women, patients with rashes, and self-reported muscle pain or weakness (Table 4). All three CT imaging patterns were reported in patients experiencing a change in diagnosis with MA screening, with 2 (14.3%), 7 (50.0%) and 5 (35.7%) patients having a definite, possible and inconsistent with usual interstitial pneumonia (UIP) patterns ($p = 0.60$). Of the patients that experienced a change in diagnosis due to MA testing, additional antibody screening results (ANA, RF and antiCCP) were negative in 8 (57.1%). The presence of PL-7 ($p = 0.0002$), PM/Scl-75 ($p = 0.02$), Ku ($p = 0.03$) and Ro-52 ($p = 0.002$) were significantly associated with a change in diagnosis. Of the 18 patients testing positive for Ro-52 antibodies, only one experienced a change in diagnosis as a result of an isolated Ro-52 antibody. When

Table 2 Characteristics of 165 patients referred with idiopathic interstitial lung disease based on the presence of myositis antibodies

	Positive myositis antibodies ($n=44$)	Negative myositis antibodies ($n=121$)	p value
Age[a] (years)	68.0 (18.5)	69.0 (13.0)	0.86
Gender [n (%)][b]			
Male	28 (63.6)	74 (61.2)	0.77
Female	16 (36.4)	47 (38.8)	
FVC—% predicted[c]	71.0 (33.1)	70.0 (23.0)	0.78
DLCO—% predicted[c]	61.0 (27.0)	75.5 (31.0)	0.01
CTD symptoms	23 (52.3)	60 (49.6)	0.76
CT pattern			
UIP	15 (34.1)	30 (24.8)	0.04
Possible UIP	22 (50.0)	47 (38.8)	
Inconsistent UIP	7 (15.9)	44 (36.4)	
Smoking status[b]			
Never	13 (29.6)	52 (43.0)	0.0002
Current	8 (18.2)	4 (3.3)	
Ex-smoker	23 (52.3)	64 (52.9)	
Raynaud's phenomenon[b]	5 (11.4)	6 (5.0)	0.16
Inflammatory arthritis[b]	3 (6.8)	5 (4.1)	0.44
GER	14 (31.8)	34 (28.1)	0.64
Rash	7 (15.9)	11 (9.1)	0.21
Sicca[b]	2 (4.5)	17 (14.1)	0.11
Sclerodactyly[b]	2 (4.5)	1 (0.8)	0.17
Muscle pain/weakness[b]	3 (6.8)	3 (2.5)	0.19
Mechanics hands[b]	0 (0.0)	0 (0.0)	> 0.99
Lung biopsy	10 (22.7)	24 (19.8)	0.68
Oxygen treatment	11 (25.0)	29 (24.0)	0.89
ANA positive	12 (27.3)	42 (34.7)	0.37
RF positive	7 (15.9)	13 (10.7)	0.56
antiCCP positive[b]	1 (2.3)	4 (3.4)	> 0.99
Creatine kinase levels[d]	72.5 (42.0)	73.0 (67.5)	0.97

ANA antinuclear antibodies (ELISA or immunofluorescence), *antiCCP* anti-cyclic citrullinated peptide, *CT* computed tomography, *CTD* connective tissue disease, *DLCO* diffusing capacity of the lung for carbon monoxide, *FVC* forced vital capacity, *GER* gastroesophageal reflux, *MA* myositis antibodies, *RF* rheumatoid factor

[a]Represents normally distributed continuous variables with the mean ± SD and interquartile range calculations, (Shapiro–Wilk < 0.05)

[b]Represents variables where the Fisher's exact test was used in univariate analysis

[c]Represents non-normally distributed continuous variables with the median and interquartile range calculations

[d]Represents variable with missing data; creatine kinase levels were available for 26 patients with positive myositis-specific antibodies and 56 patients without myositis antibodies

analysed as independent groups, both MSA ($p < 0.0001$) and MAA ($p < 0.0001$) were associated with a change in diagnosis. The sensitivity and specificity of MA screening for a change in diagnosis were calculated as > 0.99 and 0.80, respectively. The resulting negative and positive likelihood ratios for predicting a change in diagnosis due to MA screening were < 0.001 and 5.1, respectively.

Among patients that experienced a change in diagnosis due to MA screening, 3 (1.8%) patients previously underwent a surgical lung biopsy (SLB) and 2 (1.2%) had been previously prescribed antifibrotics for presumed IPF.

Discussion

After excluding patients referred with known or suspected CTD, we found MA to be common in patients with idiopathic ILD when performed as part of routine screening.

Table 3 Multivariable regression analysis for the effects of CT imaging pattern and smoking status on predicting the odds of having myositis antibodies upon screening

Predictor	Adjusted OR (95%CI)	Test statistic	*p* value
Omnibus likelihood ratio (X^2(df), *p* value)		20.79 (5)	0.0009
CT imaging			
Possible UIP vs. definite UIP	1.84 (0.72–4.74)	1.61	0.20
Inconsistent UIP vs. definite UIP	0.45 (0.15–1.33)	2.10	0.15
Smoking status			
Current vs. never smoker	6.87 (1.65–28.64)	7.00	0.008
Previous vs. never smoker	1.10 (0.49–2.47)	0.05	0.82
DLCO			
< 70% predicted	2.55 (1.09–5.97)	4.65	0.03

CT computed tomography, *DLCO* diffusing capacity of the lung for carbon monoxide *UIP* usual interstitial pneumonia

The presence of MA led to a change in clinical diagnosis in 8.5% of patients, roughly 1 in every 12 patients evaluated for idiopathic ILD.

Up to 50% of new referrals with CTD-ILD to tertiary care centre ILD clinics have been reported to have IIM [1]. Watanabe et al. diagnosed aSS in 6.6% of patients screened for MSA in a Japanese cohort, with anti-EJ antibodies being reported most frequently (3.0% of patients), and no patients testing positive for more than one MSA [4]. In contrast, we found Jo-1 and PL-7 were the most common MSA and more than one MA was present in 7.3% of patients. The addition of MAA to the screening panel performed in our study may explain the higher frequency of MA seen in this cohort. Alternatively, differences in antibody frequency may be due to genetic heterogeneity between cohorts, with certain ethnicities being more likely to develop particular MA.

Diagnosing CTD-ILD can be challenging, especially when ILD is the first manifestation of disease and additional clinical features of CTD do not manifest until later [7]. Inflammatory myositis frequently presents with lung disease prior to the onset of additional symptoms [8]. Clinicians should have a high index of suspicion for IIM when evaluating patients with ILD, carefully reviewing clinical features, CT imaging and serology. We found, age, gender and patient-reported CTD symptoms failed to predict the presence of MA, although patient-reported muscle pain and/or weakness, and rashes were associated with a change in diagnosis due to MA screening. No patients were reported to have mechanic's hand on examination in this cohort, despite 15 patients having ARS antibodies upon screening. This is similar to previous reports, where Stone et al. found 83% of patients with Jo-1 antibodies did not have mechanic's hands on examination [9]. Although helpful when present, the absence of mechanics hands should not deter clinicians from considering IIM. The limited ability of clinical features to predict MA positivity argues for a universal screening approach, ensuring the diagnosis of IIM is not overlooked or delayed.

International consensus guidelines from 2011 provided a framework for CT chest interpretation in the setting of ILD, suggesting imaging be categorised as a definite UIP, possible UIP or inconsistent UIP pattern [2]. A definite UIP pattern is predictive of UIP on SLB, and IPF in the appropriate clinical context [10]. In our cohort, the CT imaging pattern was not helpful in predicting the presence of MA after multivariable analysis. Over one-third of patients in our cohort with MA had a definite UIP pattern, with only 16% having inconsistent CT features. This differs from previous reports, where no patients with ARS antibodies had honeycombing on CT imaging [5]. Of patients who experienced a change in their clinical diagnosis as a result of MA screening, 12 (85.7%) had a possible or inconsistent CT imaging pattern. Although CTD-ILD frequently manifests as a pattern of non-specific interstitial pneumonia (NSIP), upwards of 20% of patients with CTD-ILD will have a UIP pattern on CT imaging [11]. Although it is controversial, honeycombing has been reported to develop in some patients with longstanding pathologic NSIP, which may cause an inconsistent or possible UIP pattern to evolve into a UIP pattern over time [12].

Although serology is helpful in confirming and characterising patients with CTD, nearly two-thirds of patients with MA had normal ANA, RF and antiCCP results in our cohort, suggesting clinicians should not exclude CTD based on the currently recommended serology. Aggarwal et al. reported ANA testing by ELISA to have a sensitivity of only 50% in patients with aSS, and suggested ANA testing by indirect immunofluorescence is the preferred method when evaluating for aSS [13]. Our institution performed ANA testing by indirect immunofluorescence in patients with a negative ANA by ELISA in order to maximise sensitivity. Despite this, patients with negative ANA results were found to have positive MA.

In multivariable analysis, current smoking and reduced DLCO were associated with the presence of MA. These two factors may be related, given the association between smoking and emphysema, and the development of a reduced

Table 4 Characteristics of 165 patients referred with idiopathic interstitial lung disease based on the presence of myositis antibodies screening leading to a change in diagnosis

	MA screening led to change in diagnosis ($n=14$)	MA screening did not lead to a change in diagnosis ($n=141$)	p value
Age[a] (years)	63.0 (20)	69.0 (14.0)	0.30
Gender[b] [n (%)]			
Male	4 (28.6)	98 (64.9)	0.01
Female	10 (71.4)	53 (35.1)	
FVC—% predicted[c]	69.0 (28.0)	70.5 (25.0)	0.90
DLCO—% predicted[c]	77.5 (18.5)	70.0 (33.0)	0.54
CTD symptoms[b]	11 (78.6)	72 (47.7)	0.05
CT pattern			
UIP	2 (14.3)	43 (28.5)	0.60
Possible UIP	7 (50.0)	62 (41.1)	
Inconsistent UIP	5 (35.7)	46 (30.5)	
Smoking status[b]			
Never	7 (50.0)	58 (38.7)	0.68
Current	1 (7.1)	11 (7.3)	
Ex-smoker	6 (42.9)	81 (54.0)	
Raynaud's phenomenon[b]	2 (14.3)	9 (6.0)	0.24
Inflammatory arthritis[b]	2 (14.3)	6 (4.0)	0.14
GER	5 (35.7)	43 (28.5)	0.57
Rash	5 (35.7)	13 (8.6)	0.002
Sicca[b]	0 (0.0)	19 (12.6)	0.38
Sclerodactyly[b]	0 (0.0)	3 (2.0)	> 0.99
Muscle pain/weakness	3 (21.4)	3 (2.0)	0.008
Mechanics hands[b]	0 (0.0)	0 (0.0)	> 0.99
Lung biopsy[b]	3 (21.4)	31 (20.5)	> 0.99
Oxygen treatment[b]	2 (14.3)	38 (25.2)	0.36
ANA positive	5 (35.7)	49 (34.8)	0.94
RF positive[b]	2 (14.3)	18 (11.9)	0.73
antiCCP positive[b]	1 (7.1)	4 (2.7)	0.20
Creatine kinase levels	77.0 (32.0)	68.0 (57.0)	0.20

ANA antinuclear antibodies (ELISA or immunofluorescence), *antiCCP* anti-cyclic citrullinated peptide, *CT* computed tomography, *CTD* connective tissue disease, *DLCO* diffusing capacity of the lung for carbon monoxide, *FVC* forced vital capacity, *GER* gastroesophageal reflux, *MA* myositis antibodies, *RF* rheumatoid factor

[a]Represents normally distributed continuous variables with the mean ± SD and interquartile range calculations, (Shapiro–Wilk > 0.05)

[b]Represents variables where the Fisher's exact test was used in univariate analysis

[c]Represents non-normally distributed continuous variables with the median and interquartile range calculations

DLCO in patients with combined ILD and emphysema [14]. A link between smoking and autoantibodies has been previously reported in CTD, with both RF and antiCCP antibodies being associated with smoking in rheumatoid arthritis [15]. Smoking leads to the citrullination of pulmonary proteins, and is proposed to enhance immunogenicity and contribute to disease development [16]. We found current smokers had nearly seven times higher odds of testing positive for MA than non-smokers. An association between Jo-1 antibodies and smoking has been documented previously in patients with IIM and HLA-DRB1*03 genotypes [17]. Lilleker et al. reported an increased risk of ILD in patients with IIM and a history of smoking [18]. However, no association between smoking and ARS antibodies was seen in a previous study of universal ARS screening in idiopathic ILD [5].

Surgical lung biopsies carry substantial risk, and have been associated with increased mortality in patients with CTD-ILD compared to other fibrotic lung disease [19]. We typically avoid performing surgical lung biopsies in patients with confirmed CTD-ILD as it infrequently alters treatment. We identified three patients who underwent a SLB prior to screening positive for MA who were

subsequently diagnosed with CTD-ILD following MA screening. Increased access to MA testing during the diagnostic evaluation may have prevented the need for a SLB in these cases.

The treatment of CTD-ILD is focused on managing the underlying rheumatic condition, often employing corticosteroids and immunomodulatory therapy. Antifibrotic medications have been approved for treatment of IPF, but there are currently limited data to support antifibrotics in patients with CTD-ILD. Two patients in our cohort had received antifibrotics prior to the detection of MA. In these cases, MA screening led to the discontinuation of unproven and costly antifibrotic therapy and consideration of standard of care therapy with immunosuppression. We suspect the frequency with which MA screening led to a change in diagnosis justifies the cost of MA screening in patients with idiopathic ILD, given the substantial cost of antifibrotics.

This research does have some limitations. First, we were unable to evaluate for associations between MA and mortality or lung transplantation due to a low number of events. Second, although the panel of performed antibodies in this study is larger than that sent in previous reports, [5] we did not test for all MA, failing to screen for anti-KS antibodies. Third, this study was performed at a tertiary care centre and the results may be less generalisable to non-academic centres.

We believe this study has a number of strengths. Excluding confirmed and suspected CTD cases at the time of referral and including patients with other forms of idiopathic ILD allowed for a widespread screening approach. Other research focused on the prevalence of MA in ILD patients has been susceptible to selection bias, including patients with undifferentiated CTD and only idiopathic ILD with imaging suspicious for CTD (NSIP, organising pneumonia, lymphocytic interstitial pneumonia) [20]. We also suspect the population studied here is more ethnically diverse than that previously studied, making the results more applicable to ILD physicians practicing elsewhere.

Screening for MA in patients with idiopathic ILD frequently yields positive results, and can influence patient diagnosis and subsequent treatment. Historical features and CT imaging patterns were not associated with MA, arguing for systematic screening in patients with idiopathic ILD. Routine performance of MA in addition to ANA, RF and antiCCP antibodies should be considered during the diagnostic evaluation of idiopathic ILD to enhance diagnostic accuracy, which may prevent the need for more invasive testing.

Author Contributions LF is the guarantor of this research, and takes responsibility for the integrity of this work. All authors contributed to manuscript revisions, and provided final approval of the version for publication. LF, SS and SM contributed to the study concept and design, statistical analysis, drafting of initial manuscript and study supervision. Other contributions: none.

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Compliance with Ethical Standards

Conflict of interest SS has participated in speaking engagements and advisory boards for Hoffman-LaRoche Canada, Boehringer-Ingelheim Canada and AstraZeneca Canada. He has participated in clinical trials research for Hoffman-LeRoche Canada, Boehringer-Ingelheim Canada, Prometic Pharmaceuticals, Gilead Pharmaceuticals and Sanofi-Aventis Canada. All others have no conflicts of interest to declare.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent For this type of study, formal consent is not required.

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