Interstitial lung disease in patients with mixed connective tissue disease: pilot study on predictors of lung involvement

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Competing interests: none declared.

BRIEF PAPER

ABSTRACT

Objective. Mixed connective tissue disease (MCTD) is an immune-mediated systemic disorder characterised by serum autoantibodies against U1-ribonucleoprotein and diverse multisystemic clinical manifestations. Approximately 50% of patients with MCTD develop a radiologic pattern of interstitial lung disease (ILD). Our single centre, cross-sectional study sought to identify clinical and serologic associations of ILD in patients with MCTD which may serve as predictors of lung disease and prognosis.

Methods. Patients who met the validated criteria for diagnosis of MCTD were included in the study, and were further differentiated into study and control groups based on presence or absence of ILD.

Results. Multivariate logistic regression showed an association of two clinical variables: dysphagia with an R2 value of 0.33 (p-value <0.001) and Raynaud’s phenomenon with R2 value of 0.28 (p-value <0.001).

Conclusion. An association of dysphagia with the development of ILD in our study is in harmony with the existing literature. There are primarily case reports, suggesting an association of Raynaud’s phenomenon with development of ILD in patients with undifferentiated CTD. To our knowledge, this is the first study highlighting the association of Raynaud’s phenomenon with development of ILD in patients with MCTD. The mechanistic aspects of the association between Raynaud’s phenomenon and ILD remain unexplored. The association of easily elicited historical and clinical features of MCTD with subtle, but worrisome, pulmonary pathology carries the promise of sensitising the unsuspecting clinician about the entity of ILD in MCTD.

Introduction

Mixed connective tissue disease (MCTD) was first described as a distinct systemic autoimmune disorder by Sharp et al. in 1972 (1). It is characterised by the presence of autoantibodies against uridine-rich ribonucleoprotein polypeptides (1-3). Common clinical features of MCTD include Raynaud’s phenomenon, polyarthritis, myositis, sclerodactyly, and esophageal dysmotility, with renal disease being less frequently reported compared to other systemic connective tissue diseases (4-6). Over the past few decades, studies have suggested that interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) can be serious complications of MCTD (7-10). ILD has been reported in up to 48% of MCTD patients using high-resolution computed tomography (HRCT) (11). A restrictive ventilatory pattern on pulmonary function testing (PFT) accompanying ILD in 90% of MCTD patients (6, 8, 12).

Recent descriptions of the prevalence of HRCT abnormalities in adult MCTD have ranged from 0–20% for lung fibrosis to 12–100% for ground glass attenuations (11, 13, 14). Gunnarsson et al. (15) established ILD as a common lung manifestation occurring in 66% of MCTD patients, encompassing a wide spectrum of clinical presentations ranging from patients being asymptomatic to advanced fibrosis, which was associated with a 20.8% mortality in the mean observation period of 4 years.

HRCT patterns of ILD have also varied, and have included non-specific interstitial pneumonitis, lower lobe-predominant ground-glass opacities, non-septal linear opacities, and peripheral reticulation (13, 14). Patterns of usual interstitial pneumonitis, organising pneumonia, or traction bronchiectasis are less frequent. PAH occurring in up to 45% of MCTD patients is associated with poorer outcomes (6).

There is a paucity of data on the epidemiology, pathophysiology or the clinical features of MCTD that are associated with development of ILD. Our aim in conducting this single centre, cross-sectional study was to identify clinical and serological associations of ILD in patients with MCTD which may serve as predictors of lung disease and prognosis.

Material and methods

The study population was derived from a retrospective search of patients seen in the Division of Rheumatology of Mayo Clinic in Jacksonville, Florida from 2007–2014. This study received
approval from the Mayo Clinic Institutional Review Board (approval number 14-009324). Patients were identified by computerised search using the ICD-9 code 710.9, representing undifferentiated connective tissue disease, and codes 516.31 or 516.34, representing idiopathic pulmonary fibrosis and respiratory bronchiolitis ILD, respectively. After chart review, 14 patients fulfilled the classification criteria for MCTD using the Kasukawa method (17). This method was used for all patients. All patients diagnosed with MCTD had a positive U1RNP using ELISA. The diagnosis of ILD was established after confirming a pattern of restrictive lung disease on PFT and a diagnosis of ILD either by HRCT or lung biopsy.

Demographic data and clinical features such as Raynaud’s phenomenon, myositis, arthritis, dysphagia, and smoking were also collected. Oesophageal involvement was established by confirmation of abnormalities on oesophagogastroduodenoscopy, barium swallow study, or computed tomography of the chest showing a dilated oesophagus in patients complaining of dysphagia.

A control group of 14 patients was selected using the ICD-9 code 710.9 from the same database and time range that fulfilled the classification criteria for MCTD as above. Patients in the control group did not mention nor had any evidence of respiratory symptoms on exam and therefore no specific imaging was done.

Statistical analysis
Continuous data were presented as mean (standard deviation) and categorical variables as percentage, with differences between the ILD and non-ILD groups tested using Student’s t-test and Chi-square tests. Multivariate analysis of factors associated with the presence of ILD was conducted using logistic regression, with the presence or absence of ILD as the outcome variable. To increase modelling efficiency, those covariates that reached a p-value of 0.10 or less in the univariate analysis were included in the multivariate model. Because the anti-Smith antibody was found to be highly correlated (p<0.01) with each of the other variables, it was excluded from the model. The included covariates were age, disease duration, and presence of dysphagia, Raynaud’s phenomenon, and rheumatoid factor (RF). Statistical significance was set at p≤0.05.

Results
The anti-Smith antibody occurred much more frequently in patients with ILD (57.1 vs. 7.1 percent, p=0.001). This high frequency combined with the sample size of 28 patients caused it to become the sole statistically significant covariate in the multivariate model. In order to explore the effect of other covariates on the presence of ILD, anti-Smith antibody was intentionally excluded from further iterations of the multivariate model. Doing so revealed that age, dysphagia, and Raynaud’s phenomenon were all positively correlated with the presence of ILD, whereas disease duration, the presence of arthritis, and RF were negatively (inversely) associated with ILD.

Apart from anti-Smith antibody, our study looked into clinical and laboratory variables and their correlation with ILD. Since this is a cross-sectional study, causation cannot be established ILD. The variables found to have the strongest association with ILD in our study were dysphagia with R2=0.33, p<0.001 and Raynaud’s phenomenon with R2=0.28, p<0.001.

In the univariate analysis, dysphagia alone as a symptom was found to have an association with ILD (p=0.020). Serologically, patients with anti-Smith (p=0.013) and RF (p=0.046) were found to have a statistically significant association with development of ILD. Mean age of onset of the disease and Raynaud’s phenomenon showed a non-significant difference between the ILD and non-ILD groups.

On reviewing our HRCT (high resolution Ct scans) and biopsy reports, the specific diagnosis ranged from interstitial pneumonitis with bronchiectasis to usual interstitial pneumonitis and nonspecific interstitial pneumonitis patterns. Among the Study patients, 3 had lung biopsies, 2 showing UIP pattern on histology – confirming the respective HRCT scan and one on histology showing NSIP which confirmed the HRCT scan. There were 2 HRCT scans that were read as NSIP who did not receive a biopsy and 9 that were read as interstitial pneumonitis with bronchiectasis on HRCT that also did not get a lung biopsy since it was not clinically indicated.

Discussion
Interestingly, the first publication by Sharp et al. (1) on MCTD did not re-
port any pulmonary symptoms. Bennett et al. (12) were the initial group to highlight abnormal lung function tests in their group of patients with MCTD. Since then, multiple studies have reportedILD as a relatively common pulmonary manifestation in MCTD (7, 8, 19, 20). Bodalay et al. (14) and Gunnarsson et al. (15) described the HRCT chest findings of ILD in patients with MCTD. To our knowledge, our study is the first study investigating factors that may predispose patients with MCTD to develop ILD.

To obtain the list of patients for the study, we used the ICD 9 codes as a preliminary starting point for data search. Since ICD 9 codes are very non-specific, after populating the list of patients with codes of 710.9, 516.31 or 516.34, we then performed an extensive chart review applying the criteria of Kahn or Kasukawa (16-18) to specifically include patients with MCTD in our study and control groups.

Szdoray et al. (21) published a study that assessed clinical phenotypes in MCTD patients and classified three cluster groups. In their study, 89.8% of MCTD patients with ILD have oesophageal dysmotility at the same time. This was greater than the other two clusters, wherein PAH was more associated with Raynaud’s phenomenon, and the group with anti-cyclic citrullinated peptide antibodies had more erosive arthritis.

In our study, using both univariate and multivariate logistic regression, we noted that dysphagia as a symptom is strongly correlated with the development of ILD. Other authors have also reported an association of oesophageal symptoms in MCTD patients with low diffusion capacity on pulmonary function tests and HRCT pattern of ILD (22, 23). The pathophysiological hypothesis for development of ILD in patients stems from studies done in patients with systemic sclerosis, where the associations of gastroesophageal reflux inciting ILD are well described (24, 25). Repeated insults to the lung parenchyma over time due to microaspiration of gastric acid results in fibroblast activation leading to a cascade of events that eventually predispose to development of ILD (26-28). Optimising gastroesophageal reflux and dysphagia symptoms has been suggested as a helpful strategy among the limited treatment options in patients with ILD (24).

In our study population, 10 out of the 12 patients with MCTD and ILD who experienced dysphagia were also found to have either radiographic or endoscopic evidence of a patulous oesophagus. Dysphagia and Raynaud’s phenomenon had a positive association with the development of ILD, whereas presence of arthritis in the study was seen to have a negative correlation with the development of the same. In the multivariate analysis, no serological marker stood out. Though not statistically significant, an association of ILD with onset of MCTD at an early age was also observed. Obvious limitations of our study are its retrospective nature and small study population.

Conclusions

Our study findings suggest that patients with MCTD who have clinical features of dysphagia and Raynaud’s phenomenon are more likely to develop ILD. We acknowledge that it is difficult to establish a cause and effect relationship in this study, since the number of patients is small and it is a retrospective study. It is also possible that Raynaud’s phenomenon was underreported in the non-ILD patients, all leading to a retrospective bias. The aim of the study was to find clinical associations between MCTD and ILD. As mentioned above that only an association between dysphagia and Raynaud’s can be made with regards to ILD. A longitudinal study with a larger number of patients will help remove any bias that this study may have and help confirm the associations to have a cause and effect relationship.

Whether an early comprehensive pulmonary physiological evaluation with pulmonary function testing or routine surveillance chest imaging in this subset would offer a window for earlier diagnosis of ILD and therapeutic modifications remains open to further investigation. Further prospective studies with larger cohorts are needed on this front.

References

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