Esophageal involvement and interstitial lung disease in mixed connective tissue disease

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KEYWORDS
Lung diseases; Interstitial; Mixed connective tissue disease; Computed tomography scan

Summary
Rationale: Mixed connective tissue disease is a systemic inflammatory disorder that results in both pulmonary and esophageal manifestations.
Objectives: We sought to evaluate the relationship between esophageal dysfunction and interstitial lung disease in patients with mixed connective tissue disease.
Methods: We correlated the pulmonary function data and the high-resolution computed tomography findings of interstitial lung disease with the results of esophageal evaluation in manometry, 24-hour intraesophageal pH measurements, and the presence of esophageal dilatation on computed tomography scan.
Measurements and main results: Fifty consecutive patients with mixed connective tissue disease, according to Kasukawa’s classification criteria, were included in this prospective study. High-resolution computed tomography parenchymal abnormalities were present in 39 of 50 patients. Esophageal dilatation, gastroesophageal reflux, and esophageal motor impairment were also very prevalent (28 of 50, 18 of 36, and 30 of 36, respectively). The presence of interstitial lung disease on computed tomography was significantly higher among patients with esophageal dilatation (92% vs. 45%; p < 0.01) and among patients with severe motor dysfunction (90% vs. 35%; p < 0.001).

* Impact of Research: Evaluating the most common pulmonary abnormalities and the relationship between esophageal dysfunction and interstitial lung disease in patients with mixed connective tissue disease.

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Introduction

Mixed connective tissue disease (MCTD) is a systemic inflammatory disorder in which patients have combinations of the clinical features of systemic lupus erythematosus, systemic sclerosis, and polymyositis. Patients with MCTD typically have high serum titers of antibody to extractable nuclear antigen (anti-RNP), a feature that has become the hallmark of the syndrome. Although not recognized when the syndrome was originally described by Sharp and colleagues, pulmonary involvement, mainly interstitial lung disease, is a major feature of MCTD.

The pathologic mechanisms that trigger interstitial lung disease in MCTD remain unknown. More recently, gastroesophageal reflux and repeated microaspirations have been associated with interstitial lung disease in patients with systemic sclerosis. In patients with idiopathic pulmonary fibrosis, abnormal acid gastroesophageal reflux is very common, often clinically occult. However, it is not yet possible to establish gastroesophageal reflux as a risk factor for idiopathic pulmonary fibrosis. Because pulmonary and esophageal involvements are both common in MCTD, a link between interstitial lung disease and esophageal abnormalities should be investigated. A previous study has shown an association between abnormalities in pulmonary function tests and esophageal dysfunction in the radionuclide scintigraphy (which showed a significant delay in the clearance of the nucleotide in any segment of the esophagus) in these patients.

The aim of this study was to describe the most common pulmonary abnormalities in function tests and in high-resolution computed tomography in MCTD patients and to try to establish an association between these findings and esophageal dilatation in the computed tomography scans, and between the impairment in the esophageal manometry and esophageal pH monitoring.

Methods

Fifty consecutive patients with Kasukawa’s classification criteria for the diagnosis of MCTD were included in the study (requirement for diagnosis: at least one common symptom, Raynaud’s phenomenon or swollen fingers or hands; presence of anti-U1 RNP; and one or more findings in at least two of three categories — SLE like, polyarthritis, pericarditis/pleuritis, lymphadenopathy, facial erythema and leucopenia/thrombocytopenia; scleroderma like, sclerodactyly, pulmonary fibrosis and esophageal dysmotility; and polymyositis like, muscle weakness, high creatine phosphokinase and myopathic electroneuromyography). All patients were seen as outpatients at the Rheumatology Clinic at Clinical Hospital of São Paulo (a large tertiary hospital) between January 2001 and January 2003. Each subject was invited to participate in the study and gave written informed consent. The study was approved by the Local Research Ethics Committee.

Pulmonary evaluation

Pulmonary function tests

The following pulmonary function test parameters were assessed: forced vital capacity (FVC) and forced expiratory volume at 1 second (FEV1) were measured using standard spirometric techniques. Predicted and percent predicted values were calculated for FEV1, FVC and FEV1/FVC ratio using reference values from Knudson et al. (the Knudson data set). Lung volumes, total lung capacity (TLC), and residual volume (RV) were obtained by the helium equilibration method, and were categorized as normal or low using lower limit of normal values from the reference equations of Goldman and Becklake. The diffusing capacity of carbon monoxide (DLCO) was obtained by the single-breath method, and the reference values are those of Gaensler and Wright. Data are expressed as percent-ages of predicted values.

High-resolution computed tomography of the lungs

The patients underwent both inspiratory and expiratory computed tomography scans, which were obtained with the patients in a prone position. Images were acquired from lung apices to basis with 2.0-mm collimation, 10-mm interval (inspiration), and 30-mm interval (expiration), 512 x 512 matrix. Window levels appropriate for assessment of parenchyma (level — 800 HU; window width: 1200 HU) and mediastinum (level 35 HU; window width: 650 HU) were used. A radiologist (J.K.) blinded to clinical data, results of function tests, and esophageal evaluations analyzed the computed tomography scans.

The tomographic images were evaluated to disclose radiographic abnormalities related to interstitial lung disease (based on the presence or absence of the features described below) and the presence of esophageal dilatation:

1. Ground glass opacities: areas of increased attenuation in which the bronchi and vessels remain visible;
2. Interface sign: irregularity of the interfaces between the peripheral pleura and aerated lung parenchyma, defined as subpleural micronodules or small lines perpendicular to the pleura;
3. Linear opacities: septal and nonseptal lines;
4. Bronchiolectasis or traction bronchiectasis: dilatation of the airways in the peripheral portion of the lungs;
5. Honeycombing: areas of cystic spaces (diameter < 1 cm) with thickened walls;
6. Air trapping: areas of decreased attenuation and mosaic perfusion on expiratory computed tomography;
7. Esophageal dilatation: esophagus below the aortic arch with a large collection of intraluminal air (exceeding 10 mm in the coronal plane) on 4 or more consecutive axial images. The esophagus is also considered dilated when it is fluid filled or has an air-fluid level.26

Esophageal investigations
Medications that might affect esophageal motility or acid gastroesophageal reflux (antacids, metoclopramide, cis-apride, calcium channel antagonists, theophylline, proton pump inhibitors, or histamine-2-receptor antagonists) were withheld at least 5 days prior to manometry and pH monitoring. When the examination could not be realized in the ambulatory setting, it was done in the hospital setting.

Esophageal manometry
After a minimum 8-hour fasting period and the use of topical anesthesia, the manometric probe catheter was introduced through the patient’s nose and positioned within the stomach. The 8 lumens of the polyvinyl catheter (Arndorfer model Z432) were infused with double-distilled water by a continuous infusion pump (Arndorfer Medical Specialities, Grendale, WI, USA) with a constant flow obtained by infusion of nitrogen (nitrogen pressure of 12,000 KPA). With the 4 distal side holes of the manometric tube spaced radially, the pressure at the lower esophageal sphincter was recorded. For the peristalsis evaluation, the esophageal manometric tracing was recorded with a slow pull-through of the manometric tube, centimeter by centimeter.27

Esophageal pH monitoring
After manometric evaluation, esophageal pH monitoring was done using a single catheter containing 2 antimony pH electrodes (Synetics Medical, Sweden), introduced through the nose and positioned with the distal electrode 5 cm above the lower esophageal sphincter (manometrically defined) and with the second electrode 20 cm above the lower esophageal sphincter. The catheter was externally connected to a data storage device (Digitrapper Mark III Gold, Synetics Medical, Sweden). After 24 hours, the catheter was removed, and the data transferred from the digitrapper to the computer. The analysis of data was done using Esophagram pH computer software (Synetics Medical, Sweden).

Abnormal distal and proximal gastroesophageal reflux were considered if the pH dropped to less than 4.0, for a period greater than that determined by previously published data, calculated for both the upright and recumbent periods.28

Data analysis
Statistical analysis was performed, using SPSS (Statistical Package for Social Sciences) for Windows version 11.0. Because the data were not normally distributed, statistical comparison of mean pulmonary function data (values as percentage predicted) was done using the Mann–Whitney test. For group comparisons involving binary data and to determine the significance of the differences in prevalence, we used either the chi-square test or Fisher’s exact test. p Values of less than 0.05 were considered significant.

Results
As shown in Table 1, there was a great predominance of women (49 women and 1 man), but none was pregnant. The mean age was 43 years (range, 23–66), and the mean duration of the disease was 8 years (range, 1–23). Eight subjects (16%) smoked cigarettes, but only one was still smoking at the time of entry into the study. Thirty-seven (74%) patients had typical reflux symptoms, such as heartburn or regurgitation, 30 (60%) complained of shortness of breath, and 19 (38%) had a dry cough.

Pulmonary involvement on function tests
All 50 patients had lung function assessed. Total lung capacity and DLCO were not performed in 2 and 1 patients, respectively, due to lack of cooperation during the examination. The mean pulmonary values for the group are given in Table 2.

Pulmonary involvement in high-resolution computed tomography
Fifty patients underwent computed tomography of the lungs; 39 patients (78%) had signs of interstitial lung disease on tomography: ground glass opacities (n = 36/50; 72%), interface sign (n = 22/50; 44%), subpleural linear opacities (n = 24/50; 48%), traction bronchiectasis (n = 12/50; 24%), honeycombing (n = 12/50; 24%), air trapping (n = 6/50; 12%) and consolidation (n = 2/50; 4%). Interstitial lung disease abnormalities were observed predominantly in the lower, peripheral, and posterior lung areas. They are described in Table 3.

Esophageal manometric involvement
Thirty-six patients underwent esophageal manometry. According to esophageal impairment, patients were grouped as follows: normal (n = 6/36; 16.7%); moderate dysfunction, which means patients with uncoordinated peristalsis or lower pressure wave amplitudes or distal

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical characteristics of MCTD patients.</th>
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</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>50</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>1/49</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>43 (23–66)</td>
</tr>
<tr>
<td>Median duration</td>
<td>8 (1–23)</td>
</tr>
<tr>
<td>of the disease (years)</td>
<td></td>
</tr>
<tr>
<td>Smokers or ex-smokers</td>
<td>8/50</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>19/50</td>
</tr>
<tr>
<td>Reflux symptoms</td>
<td>37/50</td>
</tr>
<tr>
<td>Patients receiving prednisone</td>
<td>38/50</td>
</tr>
<tr>
<td>Patients receiving</td>
<td>9/50</td>
</tr>
<tr>
<td>Immunosuppressive drugs</td>
<td></td>
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</tbody>
</table>

Values in parentheses are ranges.
aperistalsis ($n = 7/36$; 19.4%); and severe dysfunction or total aperistalsis of the esophageal body ($n = 23/36$; 63.9%). No significant differences existed among the groups with respect to mean age or MCTD duration.

Comparison of esophageal manometric involvement and pulmonary parameters

A difference in the presence of shortness of breath was noted among patients with aperistalsis, moderate impairment, and normal function on manometry (73.9% vs. 71.4% vs. 20%, respectively; $p = 0.03$). Patients with severe esophageal dysfunction (aperistalsis) were compared with the other two groups together (normal and moderate dysfunction) and had lower DLCO (76.4% vs. 96.6%, respectively; $p = 0.02$), but without a difference in total lung capacity (81% vs. 93%, respectively; $p = 0.08$).

Findings of interstitial lung disease on computed tomography, except for traction bronchiectasis (34% vs. 7.6%, respectively; $p = 0.1$), were more prevalent in patients with aperistalsis than in patients with moderate impairment or normal function (ground glass opacities: 95% vs. 30%, respectively, $p < 0.0001$; interface sign: 65% vs. 15%, respectively, $p = 0.006$; linear opacities, 60% vs. 30%, respectively, $p = 0.04$; honeycombing: 30% vs. 0%, $p = 0.03$), as shown in Table 4.

Comparison of esophageal dilatation on high-resolution computed tomography and pulmonary parameters

Esophageal dilatation was present in 28 patients (56%), and an example is shown in Fig. 1. Comparing the mean

<table>
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<th>Table 2</th>
<th>Pulmonary function data.</th>
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<tbody>
<tr>
<td>Variable</td>
<td>$n$</td>
</tr>
<tr>
<td>FVC%</td>
<td>50</td>
</tr>
<tr>
<td>TLC%</td>
<td>49</td>
</tr>
<tr>
<td>FEV%</td>
<td>50</td>
</tr>
<tr>
<td>FEV/VC</td>
<td>50</td>
</tr>
<tr>
<td>DLCO%</td>
<td>48</td>
</tr>
</tbody>
</table>

Values expressed as % predicted. FVC = forced vital capacity; TLC = total lung capacity; FEV = forced expiratory volume in 1 second; FEV/VC = forced expiratory volume in 1 second as % of vital capacity; DLCO = carbon monoxide lung diffusion. Values in parentheses are ranges.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Interstitial lung disease findings on HRCT in patients with aperistalsis × moderate impairment or normal function in manometry.</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRCT finding</td>
<td>Aperistalsis ($n = 23$)</td>
</tr>
<tr>
<td>Ground glass opacities</td>
<td>22 (95%)</td>
</tr>
<tr>
<td>Interface sign</td>
<td>15 (65%)</td>
</tr>
<tr>
<td>Linear opacities</td>
<td>14 (60%)</td>
</tr>
<tr>
<td>Traction bronchiectasis</td>
<td>8 (34%)</td>
</tr>
<tr>
<td>Honeycombing</td>
<td>7 (30%)</td>
</tr>
</tbody>
</table>

HRCT = high-resolution computed tomography of the lungs; ILD = Interstitial lung disease. $P$ values were determined by chi square test or Fisher exact test.

percentage values of pulmonary function data between patients with and without esophageal dilatation, significant differences existed for total lung capacity (79 vs. 92; $p = 0.009$) and for DLCO (72 vs. 100; $p = 0.004$), as shown in Fig. 2. The prevalence of interstitial lung disease on computed tomography was significantly higher in patients with esophageal dilatation (92% vs. 45%; $p = 0.001$). Computed tomography findings in patients with and without esophageal dilatation are shown in Table 5.

Gastroesophageal acid reflux

Thirty-six patients were evaluated with 24-hour esophageal pH measurements, and they were grouped according to the presence or absence of abnormal acid reflux. Eighteen patients (50%) had distal abnormal acid reflux, and 6 (16%) had acid reflux at a proximal level. The presence of severe esophageal dysfunction (aperistalsis) on manometry was not statistically significantly related to proximal ($p = 0.38$) or distal reflux ($p = 0.16$).

Comparison of gastroesophageal acid reflux and pulmonary parameters

When we compared pulmonary functional parameters in patients with normal and abnormal proximal reflux, no statistically significant differences were noted between the means of total lung capacity (84.2 vs. 89.8, respectively; $p = 0.35$) or DLCO (82.7 vs. 89.1, respectively; $p = 0.91$). In the groups with normal and abnormal distal reflux, no statistically significant differences were noted either between the means of total lung capacity (87.2 vs. 83.5, respectively; $p = 0.67$) or DLCO (81.3 vs. 86.1, respectively; $p = 0.61$).

No statistically significant differences existed in findings of interstitial lung disease on computed tomography between patients with normal and abnormal proximal reflux: ground glass opacities (21/30, 70% vs. 5/6, 83%, respectively; $p = 0.65$), interface sign (16/30, 53% vs. 1/6, 16%, respectively; $p = 0.18$), linear opacities (15/30, 50% vs. 2/6, 33%, respectively; $p = 0.66$), traction bronchiectasis (8/30, 26% vs. 1/6, 16%, respectively; $p = 1.0$), and

<table>
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<tr>
<th>Table 3</th>
<th>Signs of interstitial lung involvement in high-resolution computed tomography.</th>
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</thead>
<tbody>
<tr>
<td>Signs of interstitial lung disease</td>
<td>39/50 (78%)</td>
</tr>
<tr>
<td>Ground glass opacities</td>
<td>36/50 (72%)</td>
</tr>
<tr>
<td>Subpleural linear opacities</td>
<td>24/50 (48%)</td>
</tr>
<tr>
<td>Interface sign</td>
<td>22/50 (44%)</td>
</tr>
<tr>
<td>Traction bronchiectasis</td>
<td>12/50 (24%)</td>
</tr>
<tr>
<td>Honeycombing</td>
<td>12/50 (24%)</td>
</tr>
<tr>
<td>Air trapping</td>
<td>6/50 (12%)</td>
</tr>
<tr>
<td>Consolidation</td>
<td>2/50 (4%)</td>
</tr>
</tbody>
</table>
honeycombing (5/30, 16% vs. 2/6, 33%, respectively; $p = 0.57$).

Interstitial lung disease findings on computed tomog-
raphy were more frequent in the group of patients with
abnormal distal reflux than in patients with normal distal
pH monitoring, but without statistical significance. The
findings for these groups were, respectively, ground glass
opacities (15/18, 83% vs. 11/18, 61%; $p = 0.26$), interface
sign (10/18, 55% vs. 7/18, 38%; $p = 0.5$), linear opacities
(11/18, 61% vs. 6/18, 33%; $p = 0.18$), traction bronchiec-
tasis (7/18, 38% vs. 2/18, 11%; $p = 0.12$), and honey-
combing (6/18, 33% vs. 1/18, 5%; $p = 0.08$).

Discussion

Our findings are significant because interstitial lung
disease, gastroesophageal reflux, and esophageal motor
impairment are very common and frequently coexist in
patients with MCTD. The main signs of interstitial lung
disease (ILD) in our study were ground glass opacities (72%),
with peripheral and lower lung predominances, consistent
with previous studies.7,9 Statistically significant correla-
tions were noted between severe esophageal motor
dysfunction and evidence of interstitial lung disease on
DLCO and computed tomography. Moreover, we have shown
that the prevalence of ILD on computed tomography was
more common in patients with esophageal dilatation on
tomography scans. However, the presence of abnormal
proximal or distal gastroesophageal acid reflux was not
significantly associated with evidence of ILD, and as
a result, we were not able to attribute the correlation
between aperistalsis and lung injury to acid reflux.

Gastroesophageal reflux has been associated with
several airway manifestations, including chronic cough,
asthma, chronic bronchitis, and bronchiectasis.29–32 Two
mechanisms have been postulated to explain the relation-
ship between acid esophageal reflux and lung disease:
bronchoconstriction induced by esophageal acid and
microaspiration causing pulmonary damage.33 More
recently, gastroesophageal reflux has been postulated as
a possible causal factor in patients with ILD.13,17–19

Patients with systemic sclerosis, MCTD, and polymyositis
have a high prevalence of esophageal and pulmonary
involvements, but proving a causal relationship is difficult.
Few investigators have explored the relationship between
gastroesophageal involvement and interstitial lung disease in
systemic sclerosis, with conflicting results.11,12 Marie et al.11
found a correlation between the severity of esophageal
motor disturbances on manometry and evidence of inter-
stitial lung disease in these patients and concluded that acid
reflux may contribute to this lung injury. However, Trosh-
insky et al.12 have failed to show any correlation between
abnormal gastroesophageal acid reflux and evidence of
interstitial lung disease on pulmonary function in these
patients. Caleiro et al.21 have shown a correlation between
pulmonary abnormalities and esophageal dysfunction on the
scintigraphic evaluation and in the hystopathological
examination of the esophagus, but they could not establish
a cause–effect between them in MCTD patients.

The phenomenon of independent food and acid reflux
has been evaluated by several groups. The results obtained
from esophageal pH monitoring and those from gamma
scintigraphic detection of reflux show that there is a poor
correlation between the reflux of food and acid detected by
the 2 techniques, with significantly more reflux episodes
recorded by scintigraphy.34–37

Although in our series we did not evaluate the presence
of food reflux, it is a reasonable mechanism to explain the

Figure 1  HRCT showing esophageal dilatation in a patient
with DMTC (the esophagus has an air-fluid level).

Figure 2  Mean values and confidence intervals of DLCO (% pred) and TLC (% pred). Comparison between patients with and
without esophageal dilatation.
The work was approved by the Local Research Ethics Committee and subjects gave informed consent to it as well.

Conflicts of interest statement

The authors have no conflict of interest.

Ethics statement

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Table 5  Interstitial lung disease findings on HRCT in patients with and without esophageal dilation.

<table>
<thead>
<tr>
<th>HRCT finding</th>
<th>Normal esophagus (n = 22)</th>
<th>Dilated esophagus (n = 28)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ILD</td>
<td>10 (45%)</td>
<td>26 (92%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ground glass opacities</td>
<td>10 (45%)</td>
<td>26 (92%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Interface sign</td>
<td>6 (27%)</td>
<td>16 (57%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Linear opacities</td>
<td>7 (31%)</td>
<td>17 (60%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Traction</td>
<td>2 (9%)</td>
<td>10 (35%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Honeycombing</td>
<td>3 (13%)</td>
<td>9 (32%)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

ILD = high-resolution computed tomography of the lungs; ILD = interstitial lung disease. P values were determined by chi square test or Fisher exact test.

correlation between aperistalsis and lung damage in the absence of acid reflux. A previous study described a pattern of fibrosis, named centrilobular fibrosis, with a bronchiocentric distribution and presence of intraluminal foreign bodies, suggesting that chronic aspiration could lead to pulmonary fibrosis.38

By far from entirely resolving the controversy about the relation between esophageal dysfunction and interstitial lung involvement, our series underscores a correlation between the finding of aperistalsis on manometry and evidence for interstitial lung disease on DLCO and computed tomography. The correlation between DLCO and interstitial lung disease, but not between total lung capacity and interstitial lung disease, is probably due to the fact that reduced DLCO is the most sensitive test for predicting interstitial lung disease in these patients, preceding the reduction in total lung capacity.9

Our findings suggest that interstitial lung disease may be associated with food reflux in patients with mixed connective tissue disease, because it was more common in those with esophageal dilatation on computed tomography scan and with severe esophageal dysfunction on manometry. As a result, it strengthens the recommendation to screen regularly patients with MCTD, especially those with esophageal motor impairment, for pulmonary involvement. However, we were not able to attribute the pulmonary damage to acid reflux.

Although some authors have previously suggested that aggressive treatment of gastroesophageal reflux can decrease deterioration of pulmonary function in patients with interstitial lung disease, our results stress the need for further prospective and randomized trials to prove the beneficial effect of prokinetic therapy and proton pump inhibitors on interstitial lung disease.11,39

Conflict of interest statement

The authors have no conflict of interest.

References


