Aims and objectives

Lung involvement is common in connective tissue diseases (CTDs), an heterogeneous group of systemic immunologically mediated inflammatory disorders. [1]

As many as 25% of patients with features of a systemic autoimmune disease do not fulfill American College of Rheumatology (ACR) classification criteria for a defined CTD, such as Systemic Sclerosis, Systemic Lupus Erythematosus, Sjogren's Syndrome, Polymyositis/Dermatomyositis and Rheumatoid Arthritis. These patients are considered to have undifferentiated connective tissue disease (UCTD). [2]

The natural history of UCTD still remains unknown and unpredictable. Most of cases (65-94%) do not develop a defined CTD (stable UCTD) and are usually mild, whereas some patients can evolve over time into a specific CTD, usually within 5 years. [3]

UCTD clinical manifestations are nonspecific, including arthritis/arthralgia, Raynaud's phenomenon, skin rash and mild cytopenias. Major organ involvement is occasionally observed, but interstitial lung disease (ILD) has been frequently reported, often determining increased mortality and morbidity in this group of patients. [3]

ILD is a various group of disorders that diffusely affect the pulmonary parenchyma with inflammation and/or fibrosis; it results from variable etiologies but share common radiologic, pathologic and clinical manifestations.

To date, only few studies have investigated thoracic manifestations associated with UCTD, particularly the lung CT pattern of ILD, and significantly controversies exist; thus the interpretation of thoracic images obtained in these patients can be challenging.

High-resolution computed tomography (HRCT) is the imaging technique of choice for evaluation of the presence and extent of pulmonary parenchymal involvement, with greater sensitivity than conventional chest radiography.

The purpose of our study was to evaluate computed tomographic (CT) thoracic findings of undifferentiated connective tissue disease (UCTD) and identify the most common CT patterns of lung involvement in this condition.
Methods and materials

Study population: In this retrospective descriptive study, we reviewed CT scans obtained in 22 patients with a clinically and serologically diagnosis of UCTD who underwent a CT examination of the chest at Azienda Ospedaliero-Universitaria, Policlinico di Modena, Italy, during a mean 5 year follow up period (range 3 to 7 years).

The diagnosis of UCTD was made according to Mosca et al. [4] who proposed the following classification criteria: at least one clinical manifestation of CTDs without fulfilling the criteria of definite CTD, positive ANA (antinuclear antibodies) results and a disease duration as assessed from the onset of symptoms/signs of at least three years.

These 22 patients were identified from a clinical database provided by outpatient clinic of Rheumatology Unit of the same hospital. Our study group comprises 14 women and 8 men, who ranged in age from 32 to 83 years (mean, 64 years ± 12.9 [SD]).

All included patients underwent a CT examination of the chest because of their respiratory symptoms (dyspnea, cough and wheezing) and impairment of pulmonary function test results, particularly FVC and DLCO.

All of them are ex-smokers, except for one who is current smoker.

Data acquisition: High-resolution CT (HRCT) scans were obtained using a 64-slice scanner and were performed at baseline in all patients and followed up at a time of acute change in patient's condition.

CT scans were obtained at maximal end-inspiratory phase with patients in the supine position; additional prone scan was performed optionally. No intravenous contrast material was administered. The images were acquired using helical scanning from the apices to the lung bases with a slice thickness < 2mm. Thin-section CT images were reconstructed with an edge-enhancing algorithm and were viewed at window setting optimized for assessment of lung parenchyma (window width, 1500 HU; window level, -700 HU) and soft tissue (window width, 400 HU; window level, 40 HU).

Data evaluation: All CT images were independently reviewed in a blind manner by two radiologists with 4 years of experience, without knowledge of patient's clinical information except for the UCTD diagnosis. A third expert chest radiologist (10 years of experience) assessed each CT scan and a final decision was reached with consensus of these three radiologists.

We evaluated the following CT features of lung parenchymal involvement, separately described as present or absent, including airspace consolidation, ground-glass opacity (GGO), reticulation (irregular linear opacities), airways abnormalities (bronchial wall
thickening and parietal calcification), honeycombing, nodules, emphysema, traction bronchiectasis or bronchiolectasis, mosaic lung attenuation and air trapping.

The extent of three CT findings (reticulation, ground-glass and honeycombing) was graded with a five-point scale within the whole lung field. This scale describes the percentage of lung involvement: grade 0 (the finding was absent); grade 1 (1-25%), grade 2 (26-50%), grade 3 (51-75%), grade 4 (more than 76%).

A three-point scale was used to evaluate the extent of bronchiectasis: grade 0 (none), grade 1 (bronchiectasis localized within one bronchopulmonary segment), grade 2 (bronchiectasis extended into two or more segments).

Each patient was classified taking into account the predominant CT features and the radiologic pattern of ILD was interpreted according to the American Thoracic Society/European Respiratory Society statement on the Idiopathic Interstitial Pneumonias (2013). The CT pattern was recorded as UIP (usual interstitial pneumonia) pattern, NSIP (nonspecific interstitial pneumonia) pattern, OP (organizing pneumonia) pattern and indeterminate. [5]

The presence of additional findings was assessed, such as hiatal hernia, esophageal dilatation and pleural effusion.

The diameter of the pulmonary artery was recorded, measured at the widest diameter perpendicular to the long axis of the main pulmonary trunk, regarding as cut-off of normal pulmonary artery diameter as 29 mm. As recently reported, pulmonary artery size is accurate for detection pulmonary hypertension in patients both with and without ILD. [6]

At least, we evaluated the presence or absence of mediastinal lymph node enlargement, on the basis of criteria defined by Glazer et al. [7]

**Statistical Analysis:** Patients characteristics, CT findings of lung involvement and CT pattern were reported as frequency counts and percentages.

Interobserver agreement between the first two radiologists was determined by calculating the k value about pulmonary CT findings. The agreement was evaluated using the following scale: fair agreement (k value 0.21-0.40), moderate agreement (0.41-0.60), good agreement (0.61-0.80), excellent agreement (>0.81).
The most common CT features were those related to fibrosis: traction bronchiectasis [20 (91%) patients], reticulations [19 (86%) patients] and honeycombing [16 (73%) patients]. Airways abnormalities (68%) were also frequently seen; nodules were observed in 5 (23%) patients. All the thoracic findings found on HRCT scans of our patients are summarized in Fig.1 and Fig.2.

Interobserver agreement for the presence of HRCT features was mostly good (good to excellent agreement), except for the evaluation of GGO (moderate agreement). (Fig.3)

Reticulations, honeycombing and GGO were bilateral in most of cases and showed predominance in the lower zone of the lung; in one patient with NSIP CT pattern honeycombing was predominantly apical.

The extent of honeycombing on the baseline CT scan was grade 1 in 9 (53%) patients and grade 2 in 7 (41%) patients; during follow-up we observed an increase of one or two grades in 13 (76.5%) patients. The extent of reticulation of grade higher than 2 was the most frequent; there was a significant increase (> 25%) in 3 (14%) patients. GGO showed a grade 2 extent in the majority of cases and increased significantly in 2 patients. In most patients, traction bronchiectasis/bronchiolectasis showed an extent of grade 2.

Among 22 HRCT scans were identified 3 major CT pattern: 13 (59%) were classified as compatible with UIP, 7 (32%) with NSIP and 1 (5%) with OP; one patient was considered having the indeterminate pattern. (Fig.4)

Enlargement of the pulmonary artery was observed in 13 (59%) patients and 6 of the 7 patients with NSIP CT pattern were in this group.

Considering the accessory findings, esophageal dilatation was assessed in 8 (36%) patients and hiatal hernia in 6 (27%) patients. Moreover, half of the patients in our study group had lymph nodes enlargement.
**Fig. 1: Summary of thoracic CT Findings**

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<table>
<thead>
<tr>
<th>Finding</th>
<th>Tot n=22</th>
<th>UIP n=13</th>
<th>NSIP n=7</th>
<th>OP n=1</th>
<th>INDETERMINATE n=1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consolidation</td>
<td>1 (5)</td>
<td>1 (8)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Ground-glass opacity</td>
<td>6 (27)</td>
<td>0 (0)</td>
<td>6 (86)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Reticulation</td>
<td>19 (86)</td>
<td>12 (92)</td>
<td>5 (71)</td>
<td>1 (100)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Airways abnormalities</td>
<td>16 (73)</td>
<td>9 (69)</td>
<td>5 (71)</td>
<td>1 (100)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Honeycombing</td>
<td>16 (73)</td>
<td>13 (100)</td>
<td>2 (29)</td>
<td>0 (0)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Nodules</td>
<td>5 (23)</td>
<td>1 (8)</td>
<td>3 (43)</td>
<td>0 (0)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Emphysema</td>
<td>5 (23)</td>
<td>3 (23)</td>
<td>2 (29)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Bronchiectasis or bronchiolectasis</td>
<td>20 (91)</td>
<td>13 (100)</td>
<td>5 (71)</td>
<td>1 (100)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Air trapping</td>
<td>6 (27)</td>
<td>3 (23)</td>
<td>2 (29)</td>
<td>1 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Mosaic attenuation</td>
<td>3 (14)</td>
<td>1 (8)</td>
<td>2 (29)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Enlarged lymph nodes</td>
<td>11 (50)</td>
<td>6 (46)</td>
<td>4 (57)</td>
<td>0 (0)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Pulmonary artery enlargement</td>
<td>13 (59)</td>
<td>6 (46)</td>
<td>6 (86)</td>
<td>0 (0)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Hiatal hernia</td>
<td>6 (27)</td>
<td>4 (31)</td>
<td>1 (14)</td>
<td>1 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Esophageal dilatation</td>
<td>8 (36)</td>
<td>5 (38)</td>
<td>1 (14)</td>
<td>1 (100)</td>
<td>1 (100)</td>
</tr>
</tbody>
</table>

**Fig. 2**: CT Findings according to CT pattern. Data are numbers of patients. Data in parentheses are percentages.

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**Fig. 3:** Interobserver agreement between the two first radiologists for determination of lung CT Findings

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**Fig. 4:** CT Pattern of Interstitial Lung Disease in UCTD patients

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Conclusion

We reviewed CT scans obtained in 22 patients with a clinically and serologically diagnosis of UCTD; they underwent an HRCT examination because of their respiratory symptoms and impairment of pulmonary function test results. All of them showed a parenchymal lung involvement, particularly the finding of interstitial lung disease with different patterns.

It is commonly known that the most of ILD associated with CTD is characterized by the radiologic and histopathologic pattern of NSIP, especially in systemic sclerosis, Sjögren's syndrome and dermatomyositis/polymyositis. Otherwise, the UIP pattern has been more frequently reported with rheumatoid arthritis. [8]

In our study, NSIP CT pattern was observed in less than half of the patients, while most of them showed UIP CT pattern; it thus suggests that the predominant CT pattern in UCTD patients is UIP pattern. Our results support those of Kim et al., who concluded that in patients with ILD and UCTD the UIP pattern was as frequent as or more frequent than NSIP pattern, on the basis of radiologic and/or pathologic findings. [9]

Furthermore, ViJ et al. reported that 62% of patients with autoimmune-featured interstitial pneumonia had a typical UIP pattern on CT images. [10]

As found in our study, CT UIP pattern is characterized by the presence of reticular opacities and traction bronchiectasis with a subpleural and basal predominance; honeycombing in the posterior lung zones is critical for making a definite diagnosis. [11] (Fig. 5)

Our results are discordant from those reported by previous studies, which described the NSIP pattern as the predominant pattern in UCTD patients. For instance, Kinder et al. showed that the majority (88%) of patients classified as idiopathic NSIP (histopathologic pattern) met the criteria for UCTD; it points out that this pattern is peculiar of this disease. [8] Several authors also described the common occurrence of UCTD in NSIP biopsy-proven. [12, 13]

On the other hand, the diagnostic criteria for UCTD are different, and Kinder et al. used broader and less specific criteria compared with a stricter and accepted definition of UCTD according to Mosca et al. Thus, it might result in an overestimation of UCTD. [14]

In the current study, the most common CT findings of UCTD-related lung disease were traction bronchiectasis and reticulation related to fibrosis. These abnormalities were observed numerically equal in each CT pattern, with an overall prevalence of 91% and 86% respectively. (Fig. 6)
These results are in contrast with Kinder et al., who found that patients with UCTD-ILD were significantly more likely to have GGO on HRCT. [8] It probably correlates with the predominant CT NSIP pattern described by Kinder et al.

Other common findings were airways abnormalities, including parietal thickening and calcification, reported in 15 (68%) of 22 patients. Honeycombing was frequently seen in 16 (73%) patients; it was observed in all UIP CT pattern with a bilateral basal predominance, and in one patient with NSIP CT pattern with an apical distribution. (Fig.7)

As previously reported in association with CTD-ILD, dilatation of the pulmonary artery and lymph nodes enlargement were common accessory thoracic findings.

Concerning the extent of parenchymal abnormalities, we observed that during a mean 5 year follow up period the finding of honeycombing had the highest progression rate in 13 (76,5%) patients. It is well known that histopathological UIP patients had progressive nature irrespective of UCTD diagnosis. [14]

In our study, the interobserver agreement for determination of all CT findings was good to excellent, except for a moderate agreement for evaluation of GGO. It is probably due to difficulty in discrimination between "pure" ground-glass opacity caused by acute inflammation and hazy increased lung attenuation superimposed on a fine reticular pattern, related to fibrosis. [11] Moreover, interobserver agreement is dependent on observer experience. (Fig.8)

A limitation of our study is that pathologic findings from surgical lung biopsy were not available. However, the diagnosis of usual interstitial pneumonia (UIP) can be made with HRCT in patients with concordant clinical presentation without the need for tissue confirmation. A typical UIP pattern on HRCT is highly accurate for the presence of UIP pattern on surgical lung biopsy. [15, 16]

In conclusion, our current study findings suggest that UIP pattern is frequently seen in patients with UCTD and the most common parenchymal abnormalities are traction bronchiectasis and reticulation.

As previously reported in several studies, accurate identification of pulmonary involvement in UCTD patients has important therapeutic and prognostic implication because of the better prognosis of patients with CTD-ILD than that of idiopathic pulmonary fibrosis (IPF). [17]

Thus, a multinstitutional prospective study with a larger number of patients should be conducted in the future. Further studies should confirm our findings.
Images for this section:

Fig. 5: Bilateral basal honeycombing - UIP CT Pattern

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Fig. 6: Traction bronchiectasis/bronchiolectasis and reticulations

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Fig. 7: UIP CT Pattern: subpleural and basal predominance of honeycombing

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**Fig. 8:** Ground glass opacities and reticulations - NSIP CT Pattern

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Personal information

Stefania Ghinassi, Dipartimento interaziendale di Diagnostica per Immagini, Azienda Ospedaliero-Universitaria Policlinico di Modena (ghinassstefania@gmail.com)

Giovanni Della Casa, Dipartimento interaziendale di Diagnostica per Immagini, Azienda Ospedaliero-Universitaria Policlinico di Modena (giodc@libero.it)
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