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HRCT PULMONARY FEATURES OF ILD PATIENTS ASSOCIATED WITH CONNECTIVE TISSUE DISEASES- AN OVERVIEW

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Abstract

Introduction:Connective tissue diseases (CTDs) include a spectrum of disorders that affect the connective tissue of the human body, They include autoimmune disorders such as rheumatoid arthritis (RA), systemic lupus erythematous (SLE), scleroderma, polymyositis/dermatomyositis and mixed connective tissue disease (MCTD) characterized by immune-mediated chronic inflammation and the development of fibrosis.

In this review article we will present cases of patients diagnosed with connective tissue disorders who developed interstitial lung diseases. Rheumatoid arthritis RA-ILD in our case is presented with usual interstitial pneumonia pattern (UIP) and NSIP pattern, SLE, scleroderma, dermatomyositis, MCTD are more common presented with nonspecific interstitial pneumonia pattern (NSIP). Sjogren syndrome in our case is presented on HRCT as organizing pneumonia (OP), but we can not exclude for sure primary postinfectious cause. Lymphocytic interstitial pneumonia pattern (LIP) is also presented in one patient diagnosed with Sjogren syndrome.

Conclusion: HRCT of the lungs is a key component in the multidisciplinary approach to the diagnosis of connective tissue diseases associated with interstitial lung disease. The evaluation of radiological lung changes in correlation with clinical data not only leads to a correct diagnosis in many cases, but in this context plays an important role and helps in determining the prognosis, monitoring the effectiveness of treatment, detecting disease progression or complications, and evaluating patients with worsening or acute symptoms.

Key words: Connective tissue diseases, ILD, HRCT, lungs, UIP, NSIP, OP, LIP

Introduction

Collagen vascular diseases(CVDs) refer to a group of autoimmune disorders including rheumatoid arthritis (RA), systemic lupus erythematous (SLE), scleroderma, polymyositis/dermatomyositis and mixed connective tissue disease (MCTD) [1].

It is a group of acquired immunologically mediated inflammatory disorders that affect the connective tissue of many organs, including the lungs.

Connective tissue diseases (CTDs) include a spectrum of disorders that affect the connective tissue of the human body; they include autoimmune disorders characterized by immune-mediated chronic inflammation and the development of fibrosis.[43] The frequency of intrathoracic manifestations and the pattern of abnormality vary, depending on the underlying CVD. Pulmonary abnormalities seen in these patients may be due to the underlying CVD or may be due to complications of treatment, such as opportunistic infection and drug toxicity.

The most important intrathoracic manifestations of CVDs are diffuse interstitial lung disease (ILD) and pulmonary hypertension, which together account for most of the morbidity and mortality in these patients.[4] In some CVDs, such as progressive systemic sclerosis, ILD is common, eventually developing in 70%-100% of patients, while in other CVDs particularly SLE, ILD occurs in <10% of patients.[2,3].

The most common histopathologic patterns of ILD seen in the setting of CVDs are nonspecific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP), organizing pneumonia (OP), and lymphocytic interstitial pneumonia (LIP).

Approximately 30 % of patients with newly diagnosed ILD have underlying collagen vascular disease, although the exact frequency of collagen vascular disease-associated ILD is unknown. Up to 90% of patients with collagen vascular disease will have pulmonary involvement. ILD prevalence on high-resolution computed tomography (HRCT) is 70%-90% in systemic sclerosis, 4%-68% in

rheumatoid arthritis, 20%-85% in mixed connective tissue disease, 10%-30% in Sjogren's syndrome, and up to 30% in systemic lupus erythematosus. Due to this high prevalence of CTD-ILD, most guidelines recommend excluding connective tissue disease in newly diagnosed ILD.[71]

High-resolution computed tomography (CT) is superior to chest radiography in the detection of ILDs and is more accurate in the differential diagnosis and distinction of potentially reversible abnormalities from irreversible fibrosis. High-resolution CT is therefore commonly used in the initial evaluation and follow-up of patients with CTD and clinically suspected or proven ILD.[4]

Nonspecific interstitial pneumonia (NSIP)

NSIP began to attract attention in 1994 when Katezenstein and Fiorelli described histological findings that did not fit the traditional classification of interstitial pneumonia. It most often manifests as pulmonary symptoms associated with connective tissue diseases, especially rheumatoid arthritis, scleroderma, dermatomyositis, systemic lupus, etc.[5].

Patients with NSIP pattern are more likely to be younger and predominantly female, between 40 and 50 years of age. Symptoms are similar to, but milder than, those of Idiopathic pulmonary fibrosis. They have an overall better prognosis with fewer exacerbations compared with usual interstitial pneumonia and a median survival of greater than 9 years.

Treatment involves therapy of the underlying disease in combination with corticosteroids and cytotoxic drugs, which are successful in most cases.[7].

NSIP is characterized histologically by homogeneous inflammation and expansion of the alveolar walls with or without fibrosis and can be classified into three subtypes: cellular (less common and with a better prognosis); fibrotic (with a worse prognosis); or mixed.

The extent of the disease can be measured visually and is marked by progression as the volume of the normal lung decreases [5]. In some patients, progression from nonfibrotic cellular NSIP with its predominant ground-glass attenuation to mixed cellular and fibrotic NSIP with ground-glass attenuation, bronchiectasis, and eventually fibrotic NSIP with resolution of most of the ground-glass opacities plus honeycombing may be described radiologically.[8] Mortality approaches that of idiopathic pulmonary fibrosis (IPF) if honeycombing is present.

The HRCT distribution tends to be subpleural and generally symmetrical with an apicobasal gradient. Typical manifestations include: ground glass changes as the dominant feature, which may be symmetrical or diffusely distributed in all zones or show basal predominance; immediate subpleural sparing is a relatively specific sign.

Ground glass opacities are mainly bilateral and symmetrical (86%), but may also be bilaterally asymmetrical (10%) or rarely unilateral (3%), reticular opacities, thickening of bronchovascular contours, traction bronchiectasis, loss of volume, while microcystic honeycombing is a less specific feature [9, 10].

NSIP is presented as a homogeneous, dominant type of fibrosis in the lower lung, and newly described specific HRCT findings are concentration of fibrosis in the anterior aspect of the upper lobes (with sparing of other parts of the upper lobes) – “anterior upper lobe sign” and concomitant involvement of the lower lobes; exuberant cystic formations in the form of a honeycomb lung that occupy 70% of the fibrotic lung changes (“exuberant honeycomb-like cyst sign”); isolation of fibrosis at the lung bases with a sharp demarcation in the craniocaudal plane and without substantial extension along the lateral margins of the lungs in coronal images (“straight –edge” sign)[6].

However, despite the presence of characteristic HRCT signs that often allow a reliable diagnosis, the same cannot be said with certainty and accuracy when establishing between NSIP and UIP pattern in the absence of honeycombing when surgical biopsy or another multidisciplinary approach is required for definitive diagnosis [11].

NSIP pattern

Antisynthetase syndrome

Figure 1.

Figure 2.

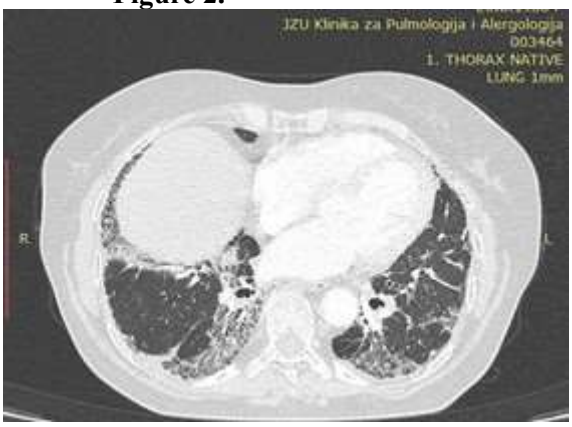
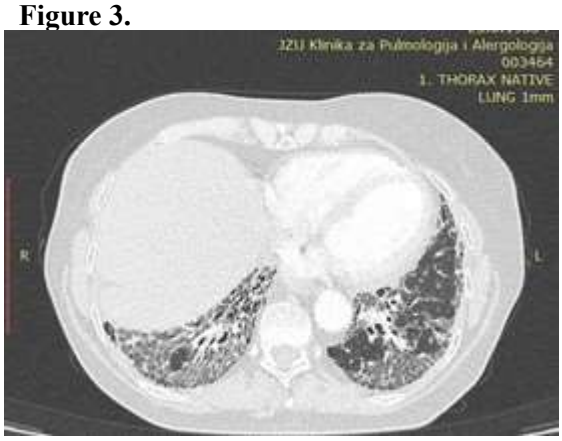
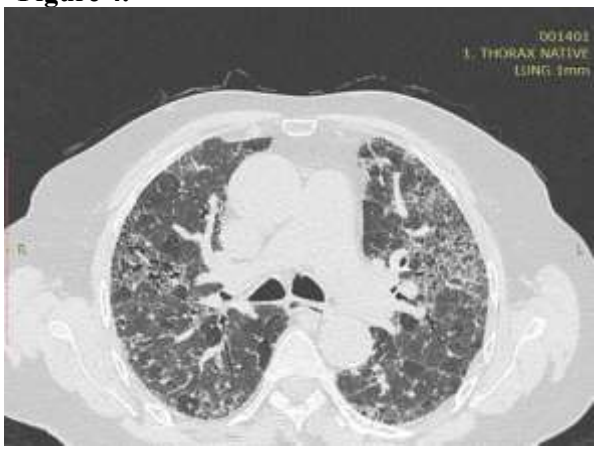


Figure 3.



Systemic lupus erythematous (SLE)

Figure 4.



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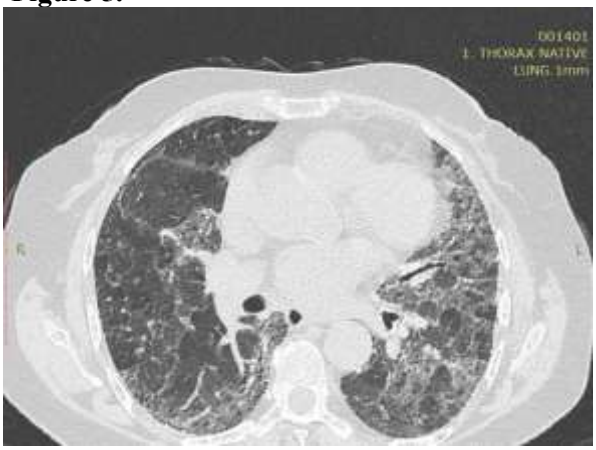

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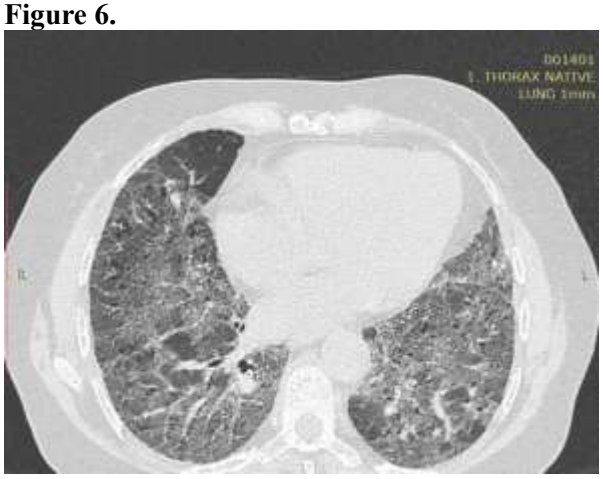


Scleroderma

Figure 7.

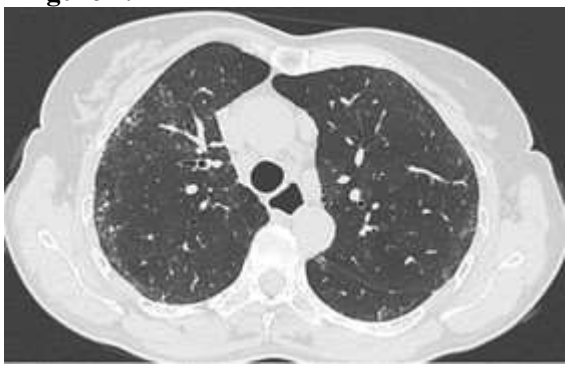
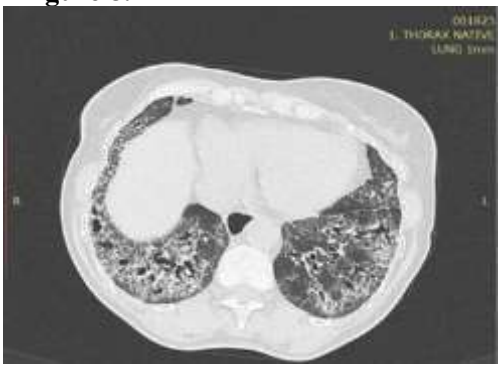


Figure 8.



SLE and Scleroderma

Figure 9.

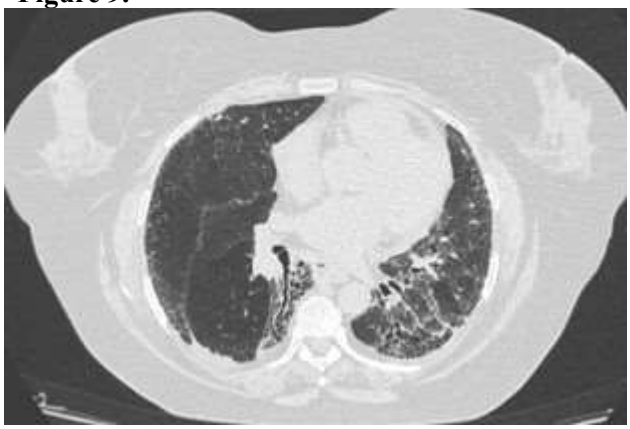
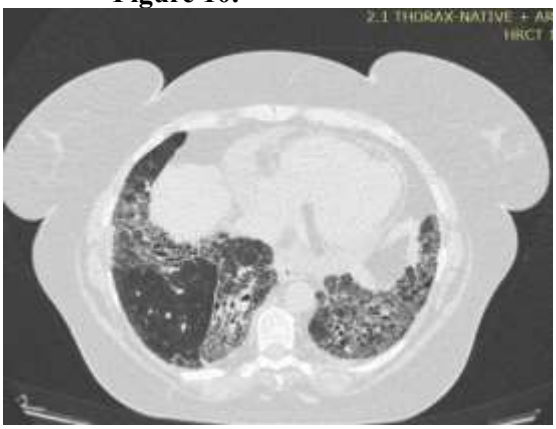
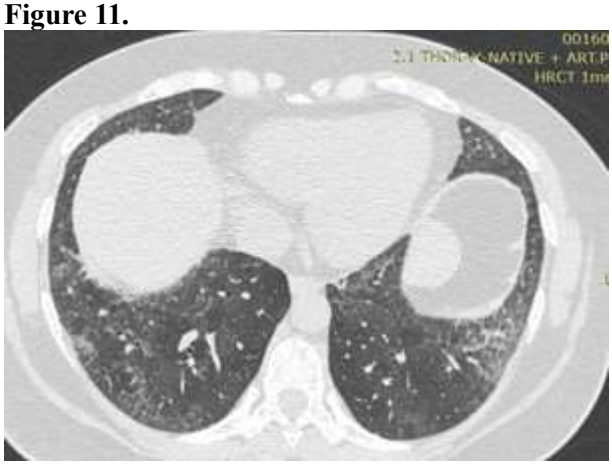


Figure 10.



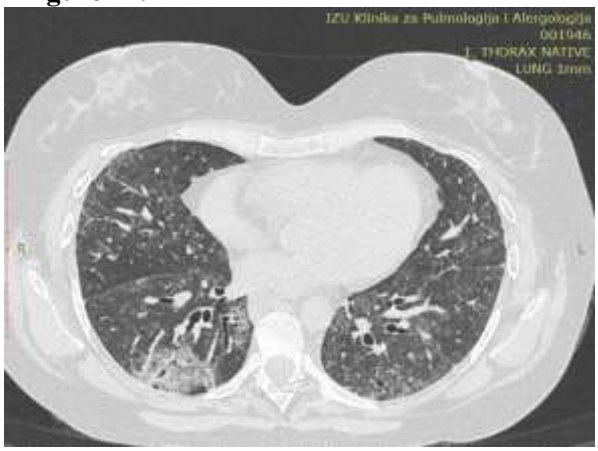
Reynaud syndrome + PM

Figure 11.



Dermatomyositis

Figure 12.



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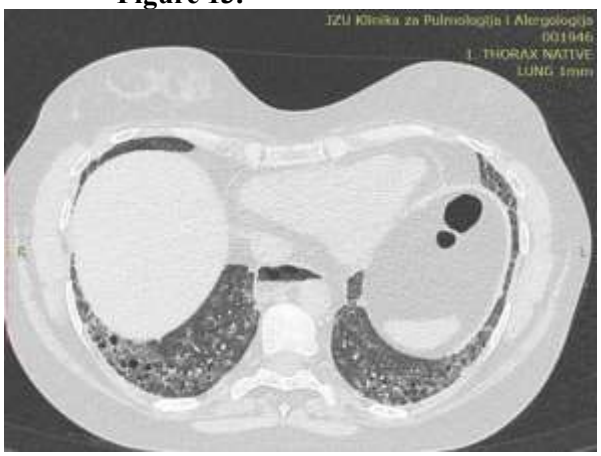
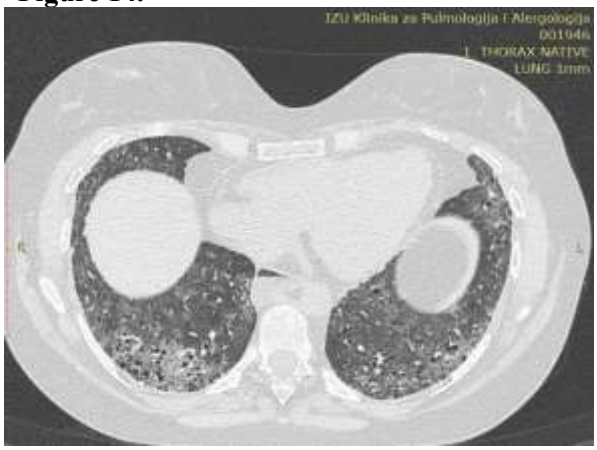


Figure 14.



NSIP-RA-PM-Overlap

Figure 15.

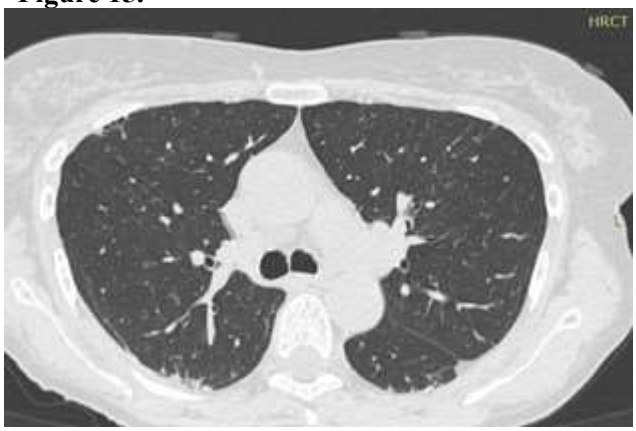
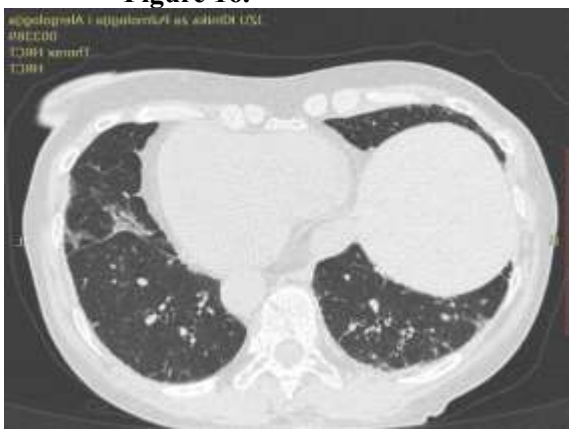


Figure 16.



Usual interstitial pneumonia (UIP)

UIP pattern on HRCT is often associated with a clinical diagnosis of idiopathic pulmonary fibrosis (IPF), which has a life expectancy of 3–4 years without treatment [12].

Patients with UIP pattern are most often older men who smoke [13]. This pattern carries a poor prognosis and an increased risk of death regardless of the underlying cause. Acute exacerbations of the findings are also more common. The UIP pattern does not automatically mean a diagnosis of IPF, as other interstitial lung diseases can have the same pattern on HRCT. Drug intoxication, ***collagen vascular diseases***, and familial pulmonary fibrosis can also have this pattern. They have a longer survival period than IPF, but mortality is similar if honeycombing is present radiologically [14].

The characteristic HRCT finding of UIP includes reticular opacities with honeycombing cysts, often accompanied by traction bronchiectasis. Ground-glass opacity is much less common than reticular opacities. The changes are characteristic of the basal and peripheral subpleural lung regions. On HRCT, honeycombing of the lung contains clustered cystic air spaces typically 3–10 mm in diameter, although they can be seen as large as 2.5 cm. They have well-defined walls, and need to be distinguished from emphysematous changes [15].

The HRCT finding consisting of a definite UIP pattern may be asymmetric in up to 25% of the findings in UIP patients. The right lung is more commonly affected. This distribution is more common in UIP than in other fibrotic lung diseases [16].

Rheumatoid arthritis (RA) is a systemic inflammatory disease that affects approximately 1% of the population,1 and pulmonary involvement is common.[17]

Interstitial lung disease (ILD) is the primary pulmonary manifestation of RA, as it is for other connective tissue diseases. RA-associated ILD (RA-ILD) is a source of substantial morbidity and mortality for affected patients. The histopathologic and radiographic appearance of RA-ILD is heterogeneous and primarily mimics the following two patterns seen in the idiopathic interstitial pneumonias (IIPs): usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP).

Distinguishing UIP from NSIP has important prognostic implications. Idiopathic UIP (ie, idiopathic pulmonary fibrosis [IPF]) has a uniformly poor prognosis and lacks an effective medical therapy; idiopathic NSIP has a better prognosis and often responds to anti-inflammatory therapy. Moreover, IPF, which is characterized by abnormal wound healing and abnormal epithelial cell function, is thought to have a distinct pathobiology from NSIP. Because of this, the diagnostic workup of patients with IIPs emphasizes the histopathologic and radiographic identification of UIP. In many cases, radiographic imaging is sufficient,8 and surgical lung biopsy is required only for those patients in whom radiographic imaging is nondiagnostic.[18,19]

RA-UIP

Figure 17.

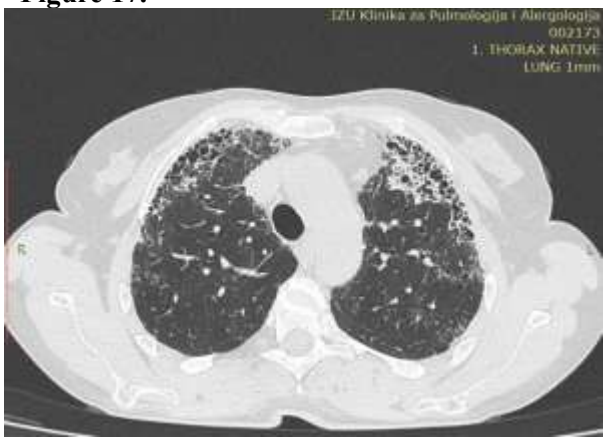
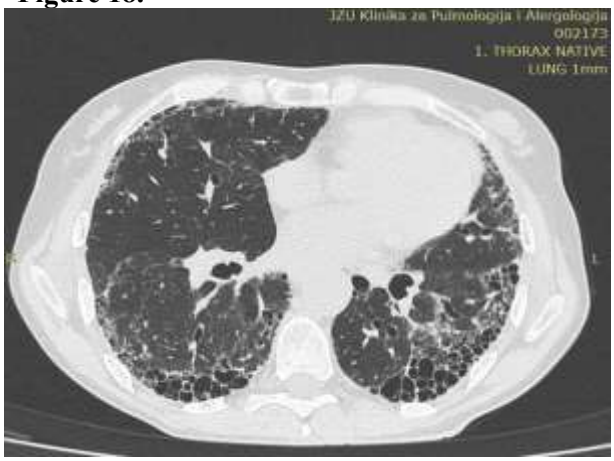


Figure 18.



Organizing pneumonia (OP)

Organizing pneumonia (OP) is an interstitial pneumonia with an acute or subacute clinical course and a histological pattern compatible with acute lung injury. It usually occurs after a recent infection of the peripheral bronchial system, in which case it is called secondary OP. When it occurs without an identifiable cause, it is called cryptogenic organizing pneumonia (COP). Until 2000, the name idiopathic bronchiolitis obliterans with organizing pneumonia (BOOP) was used synonymously [20]. To better differentiate it from bronchiolitis obliterans syndrome, which is a well-known and common pulmonary complication of allogeneic stem cell transplantation that can sometimes accompany or precede BOOP, the term COPD was preferred in part because this pathology is more common in other clinical settings.

For practical purposes, a distinction is made between primary COPD without a specific etiology and secondary OP. The latter may be medically induced, infectious, or associated with vasculitis or malignancy [21,22].

It occurs most commonly between the ages of 55 and 60 in both sexes with symptoms such as shortness of breath lasting less than two months, nonproductive cough, weight loss, malaise and fever. There is no association with smoking[24].

Within a few days, the patient develops hyperthermia and shortness of breath, which may progress to signs of inflammation and an increase in the level of neutrophils in the blood. Bronchoalveolar lavage is nonspecific, but often shows an increase in lymphocytes. Symptoms resolve

rapidly with steroid therapy, but may return when treatment is stopped or progress to a chronic and fibrosing form that carries a worse prognosis [23].

High-resolution computed tomography (HRCT) demonstrates a variety of changes in COPD. Typically, COPD is sharply demarcated from the surrounding parenchyma with a lobular pattern adjacent to the bronchovascular structures. This is an important imaging finding to differentiate it from other infectious processes, e.g. bronchopneumonia, which shows a fluctuating or indistinct border surrounded by normal lung parenchyma. In COPD, there is usually no evidence of parenchymal destruction. Bilateral infiltrates with rounded or flat areas of consolidation accompanied by ground-glass opacities are common[25].

Other common radiological findings of the lungs include bilateral cloudy areas of consolidation that show a predominance subpleurally and towards the lower lung zones. HRCT findings consist of consolidation areas or nodules distributed along bronchovascular structures or along subpleural regions [26-29]. Parenchymal consolidation is the most common HRCT finding (80–95%), often accompanied by an air bronchogram. Parenchymal consolidations often change their distribution and location during the course of the disease, i.e. they migrate. In distribution, peripheral and basal regions are often involved, especially together with bronchial vascular structures that have a lobular pattern. The predominance in the lower lung lobes helps to distinguish COPD from chronic eosinophilic pneumonia, which is usually encountered in the upper lung zones [25].

The emergence of OP in the context of connective tissue disease is considered to be a poor prognosis factor [69]. Among connective tissue diseases, OP has been reported mostly in rheumatoid arthritis, less frequently in secondary Sjögren's syndrome, rarely in primary Sjögren's syndrome (PSS) and systemic lupus erythematosus, and exceptionally in systemic sclerosis [70].

Figure 19.

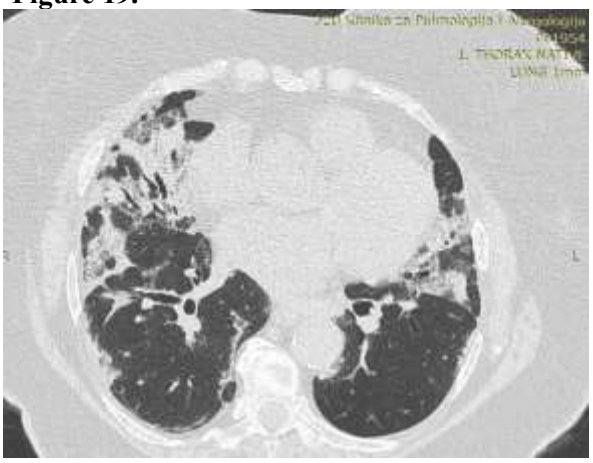
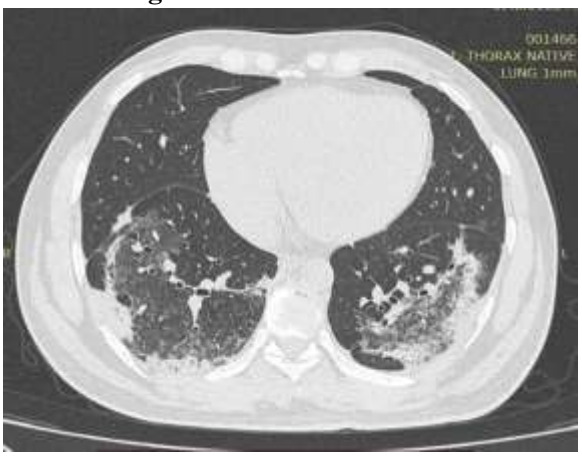


Figure 20.



Lymphocytic interstitial pneumonia (LIP)

Lymphoid interstitial pneumonia (LIP), also known as lymphocytic interstitial pneumonitis, is a benign lymphoproliferative disorder characterized by a predominant lymphocytic infiltration of the lungs. It is classified as a subtype of interstitial lung disease. It also falls under the umbrella of nonlymphomatous pulmonary lymphoid disorders. LIP can occur at any age, but most patients are adults with a mean age of 52–56 years. If a child has LIP, it may be indicative of AIDS [30].

There is an established female predilection (~2-fold) that is likely attributable to the fact that LIP occurs in patients with autoimmune diseases such as Sjögren's syndrome, which is much more common in women [31].

The main clinical symptoms are: gradual onset of dyspnea and cough with a duration of approximately 6 months. Less commonly, patients may have systemic symptoms such as fever, night

sweats, arthralgia and weight loss. If the disease progresses to end-stage respiratory failure, cyanosis and clubbing may develop. Salivary gland hypertrophy may be observed in 20% of patients [32].

The course and prognosis are variable, ranging from near-complete resolution to progressive disease. More than 30% of patients will develop end-stage disease and honeycombing despite treatment. According to some reports, the 5-year mortality may range from 33–50% [33]. Transformation to lymphoma may occur in about 5% of cases, especially in patients with monoclonal gammopathy or hypogammaglobulinemia [34, 35].

HRCT changes tend to be diffuse with a predominance of the middle to lower lobes with thickening of bronchovascular structures, interstitial thickening along lymphatic channels, pulmonary nodules of small but variable size (can be centrilobular or subpleural and are often irregular), thin-walled cystic lesions dispersed without a particular predilection (scattered), and mediastinal lymphadenopathy [33,36,37].

Histopathological lymphoid interstitial pneumonia is an uncommon interstitial lung disease, with the idiopathic form being extremely rare. Similar to other interstitial lung diseases, physiologic restriction and abnormal gas exchange are common, and the expected lymphocytosis in bronchoalveolar lavage is present. Clinical stability or improvement in response to corticosteroids may be expected, but survival is questionable. Large multicenter trials are needed to further understand this disease. [38]

Figure 21.

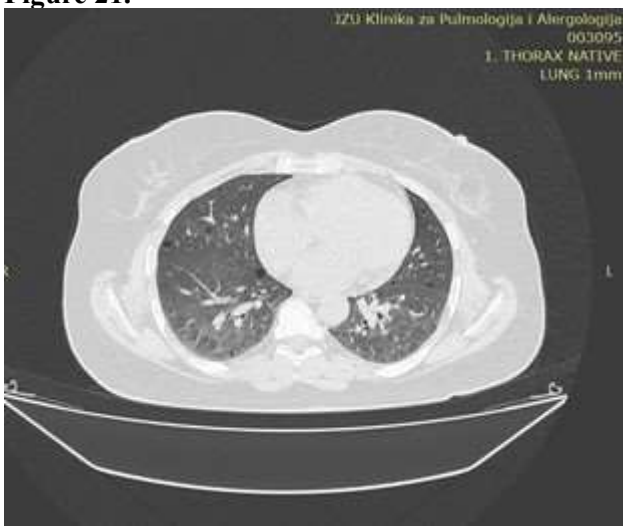
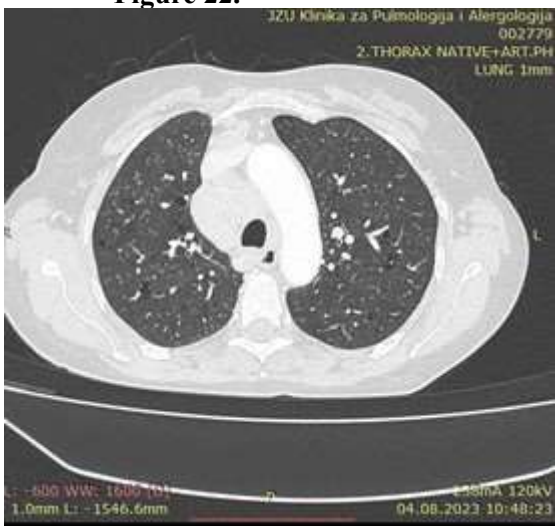


Figure 22.



Differential diagnosis and prognosis

Other entities that cause interstitial lung diseases, such as sarcoidosis and occupational disorders, must be considered. Acute viral pneumonia, including COVID-19 pneumonia, may also appear clinically and radiologically similar to acute exacerbation of interstitial lung disease. Cardiogenic and non-cardiogenic pulmonary edema may cause diffuse alveolar and interstitial opacities with interlobular septal thickening that may simulate interstitial lung disease[39]

Collagen vascular disease-associated interstitial lung disease is associated with significant morbidity and mortality. Collagen vascular disease-associated interstitial lung disease typically bears a better prognosis than idiopathic interstitial lung disease and a slower progression than idiopathic pulmonary fibrosis. The mortality rates are similar among various connective vascular disease-related-ILD (including rheumatoid arthritis, scleroderma, polymyositis, and dermatomyositis-related ILD) and remained steady over the last two decades[40]

Discussion

Interstitial lung diseases are a heterogeneous group of characteristic lung diseases classified on the basis of radiological, clinical and pathological factors that, at different stages of the disease, cause fibrotic changes in the lung tissue [1].

This collection of diseases has different causes and different treatments, and it is very important to distinguish IPF from other types of lung diseases. Some conditions are idiopathic, others are caused by viral infections, then by multifactorial agents of the external and occupational environment, and some are correlated with connective tissue diseases. Numerous studies note that they are associated with increased mortality and show radiological progression, which is why their timely recognition is necessary. Each of these entities has unique radiological findings, but often with overlapping patterns of changes seen on HRCT.

Some patients with UIP pattern show the same HRCT features as NSIP. Sumikawa et al reported that nearly 30% of patients with biopsy-proven UIP show the same appearance as those with NSIP [65].

ILD is a common extraarticular manifestation of **rheumatoid arthritis**. While the NSIP pattern predominates in most cases of connective tissue disease, studies of patients with RA associated with ILD suggest that the UIP pattern is much more common in this type of disease. HRCT is suitable for identifying the UIP pattern in many patients with RA associated with ILD. (Figs. 17 and 18). Although data are limited, the UIP pattern appears to be associated with a significantly worse survival rate in patients with RA-ILD [84].

Myositis-related interstitial lung disease presents with a wide variety of lesions, ranging from chronic to acute. It can be divided into two main forms by the types of onsets, namely, chronic to subacute type showing nonspecific interstitial pneumonia (NSIP) (Figs. 12,13,14) or NSIP with an organizing pneumonia (OP)/fibrosing OP (FOP) pattern and acute type showing acute lung injury (ALI) to diffuse alveolar damage (DAD) pattern. Anti-aminoacyl tRNA Synthetase antibody-positive cases mainly show an NSIP or FOP pattern. Bilateral consolidation with or without ground-glass opacification with lower lobe predominance is common as a major pattern in all types, but the distribution or extent is sometimes different.[41,42]

Considering the chronic interstitial disease—as with other CTDs—NSIP represents the most frequent radiological and pathological pattern encountered in **Systemic lupus erythematosus**, followed by LIP and OP; the UIP pattern is very uncommonly reported [51]. Bronchiolitis obliterans has been also reported as the initial manifestation of SLE [69].

Radiographic evidence of interstitial fibrosis in SLE patients is characterized by a reticular pattern, predominantly in the lower lobes and is seen in only about 3% of patients. Instead, HRCT interstitial abnormalities are seen in 30% of patients; they are often relatively mild and non-specific, with thickening of interlobular and intralobular septa and parenchymal bands being the most frequently observed [44] (Figs. 4,5,6). Honeycombing is uncommonly seen in SLE. Other findings include GGO and consolidations, reflecting not only the presence of a wide spectrum of patterns such as interstitial fibrosis, but also the presence of ALP, DAH, or OP.

Parenchymal lung involvement is very common in patients with **scleroderma**. At autopsy, the lungs are abnormal in at least 80% of cases. Lung fibrosis is the most common pattern of abnormality, with NSIP being much more common than UIP. However, pulmonary hypertension is also common, either as an isolated finding or in association with lung fibrosis. Pulmonary hypertension is particularly common in patients with limited scleroderma (CREST syndrome). Esophageal dilation is found in up to 80% of cases on CT.[44](Figs.7,8)

CT findings in scleroderma reflect the dominant NSIP histology, and are characterized by confluent ground glass opacification and fine reticular pattern, often posterior and subpleural, usually associated with traction bronchiectasis and bronchiolectasis[45,46] Honeycombing, when present, is usually mild.[47] However, patients with honeycombing on initial CT are probably more likely to progress on serial evaluation [46]. The lung fibrosis associated with scleroderma is associated with a much better prognosis than that found in idiopathic lung fibrosis[48-50] most likely due, in part, to the predominant NSIP histology. In a large treatment study, the extent of lung fibrosis identified on baseline CT was an important independent predictor of physiologic progression, and of response to treatment.[51]

Mixed connective tissue disease (MCTD) is an overlap syndrome that is a distinct clinicopathological entity.The principal characteristics are the presence of (1) features of SLE,

scleroderma, (Figs.9,10) PM/DM (Figs.11), occurring together or evolving sequentially during observation; and (2) antibodies to an extractable nuclear antigen (RNP).[52]

Pulmonary involvement is common in MCTD. A study of 144 unselected patients found CT evidence of infiltrative lung disease in 67%.[53] Many affected patients are asymptomatic. The pulmonary abnormalities resemble those seen in SLE, SS, and PM/DM.Thus, pleural thickening and pleural and pericardial effusions are common.[54] Ground glass attenuation is the most common parenchymal abnormality.[53,55] The CT pattern corresponds most closely to NSIP (Figs.15 and 16). Less common findings include honeycombing, consolidation, and poorly defined centrilobular nodules.

Anti-synthetase syndrome is an idiopathic inflammatory myopathy that is characterized by inflammatory myositis, polyarthritis, interstitial lung disease, and anti-synthetase autoantibodies. It is considered a distinct entity to dermatomyositis.[56] The associated interstitial lung disease of anti-synthetase syndrome usually gives either a NSIP pattern, an organizing pneumonia (OP) pattern or a combination of the two (NSIP-OP pattern) [57] (Figs. 1,2,3). A UIP pattern may also occasionally occur [58]. The consolidative regions may decrease or resolve in many cases although the disease can at times progress to fibrosis in more than one third of patients.

HRCT of the chest is the gold-standard imaging for detecting ASyS-ILD, revealing unique imaging patterns compared to other causes of ILD. Waseda et al. described these features as ground-glass opacities, consolidation, and reticulation, distributed in the lower lobes, periphery, and/or peribronchovascular regions, most consistent with NSIP. The NSIP pattern alone was found in >55% of ASyS-ILD cases. The remaining cases consisted of an OP pattern (marked by patchy areas of peripheral, subpleural, and peribronchiolar consolidations) or a mixed NSIP/OP pattern [59]. The usual interstitial pneumonia (UIP) pattern (marked by honeycombing and traction bronchiectasis) has also been described but is less frequent than NSIP [59,60,61].

Sjogren's syndrome is a disease primary affecting exocrine glands, with ILD representing a major extraglandular manifestation[62]. Studies have found a wide range in the prevalence of ILD, from 25%-40%[62-64]. As with other CVD-associated ILD, the presence of ILD is associated with poor survival[62]

The most common pathology pattern is NSIP, but UIP, OP, and LIP can be present as well[65,66,67,68] (Figs.19 and 20). The typical HRCT findings are consistent with NSIP, patchy ground glass and microcystic honeycombing predominantly in the lower lobes. When LIP is present, the HRCT shows ground glass, cysts (5-30 mm), and peribronchovascular, centrilobular, and subpleural nodules. Other findings that can be seen patients with Sjogren's syndrome in general are bronchial wall thickening, bronchiectasis, air trapping, cysts, and nodules[44] (Figs.21 and 22)

Conclusion

HRCT of the lungs is a key component in the multidisciplinary approach to the diagnosis of connective tissue diseases associated with interstitial lung disease. It also plays an important role in the follow-up of patients and provides valuable information that cannot be determined from the clinical history or other diagnostic tests, such as pulmonary function tests.

The evaluation of radiological lung changes in correlation with clinical data not only does not lead to a correct diagnosis in many cases, but in this context plays an important role and helps in determining the prognosis, monitoring the effectiveness of treatment, detecting disease progression or complications, and evaluating patients with worsening or acute symptoms. HRCT plays a central role in the diagnosis of interstitial lung diseases and is an integral part of the evaluation of patients with diffuse lung diseases.

When the radiologist is confronted with diffuse interstitial lung disease, the identification of honeycombing or peribronchovascular opacities allows the working diagnosis to be accurate in over 90% of the analyzed images. In the case of lung cysts, the accuracy ranges from 80-89%. Although ground glass attenuation when present in isolation is of little help in the characterization of the lesions, when these changes are seen in combination with other characteristic lesions, such as honeycombing or a predominant distribution in the lower zones, the probability of an accurate diagnosis is high.

Identification of these patterns, especially in UIP and their association with specific diseases allows for a definitive diagnosis, without the need for biopsy, especially when there is a correlation between the observed patterns and clinical data.[52]

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