International Journal of
Science Inventions Today
www.ijsit.com
ISSN 2319-5436
Review Article

CRYPTOGENIC ORGANIZING PNEUMONIA AND CONNECTIVE TISSUE ASSOCIATED INTERSTITIAL LUNG DISEASE: A COMPARISON

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ABSTRACT

Cryptogenic organizing pneumonia (COP) and connective tissue disease associated interstitial lung disease (CTD-ILD) are two different sub-types of interstitial lung disease (ILD) that have a relative overall good prognosis than other types of ILDs. The clinical presentation of dry cough and exertional dyspnea are common in both disease types although the frequency of lung manifestations in CTD-ILD varies according to the type of connective tissue disease (CTD). High resolution computer tomography (HRCT) most of the time confirms the diagnosis in both. Pulmonary function tests mostly reveal a restrictive pattern. Corticosteroids is the mainstay treatment for COP while CTD-ILD might not require treatment but in severe and/or progressive disease require corticosteroid with or without other immunosuppressive therapy. In this article, we review the clinical manifestations, management and prognosis of COP and CTD-ILD.

Keywords: Cryptogenic organizing pneumonia, Connective tissue disease, Interstitial lung disease, Rheumatoid arthritis, systemic sclerosis, radiology, management

INTRODUCTION

Interstitial lung disease (ILD) is a group of lung diseases in which the interstitium of the lungs are affected [1]. ILD is an important disorder disabling the lungs and is being increasingly recognized all over the world [2,3]. Interstitial lung diseases cause thickening of the interstitium due to inflammation, scarring, or extra fluid (edema). Some forms of interstitial lung disease are short-lived; others are chronic and irreversible. Nearly half of the patients with interstitial lung diseases have underlying secondary causes.

The classification of interstitial lung inflammation has gained widespread acceptance [4]. According to the American Thoracic Society (ATS) and the European Respiratory Society (ERS), cryptogenic organizing pneumonia (COP) is a subtype of idiopathic interstitial pneumonia [5]. Connective tissue disease associated interstitial lung disease (CTD-ILD) is a group of interstitial lung diseases secondary to various connective tissue diseases (CTD), mainly secondary to systemic sclerosis (SSc), rheumatoid arthritis (RA), polymyositis/dermatomyositis (PM/DM), Sjögren's syndrome (SjS), systemic lupus erythematosus (SLE), and mixed connective tissue diseases (MCTD) [6,7,8]. Both COP and CT-ILD have better prognosis than other types of ILDs. In this review, we tried to compare the clinical features, radiological findings, management features and prognosis of COP and CTD-ILD and proceed to highlight some of the important aspects of differentiating the two types of ILD.

Clinical features:

The common clinical presentation of COP and CT-ILD include cough and dyspnea except that CT-ILD have extra-thoracic manifestations and symptoms depending on the underlying connective tissue disease. COP classically presents with nonspecific systemic (e.g., fevers, chills, night sweats, fatigue) and respiratory (e.g. difficulty breathing, cough) symptoms which is usually subacute. The prevalence of COP between males and females are almost equal and are usually aged between 50 and 60 years [9,10,11]. The most common presentation includes persistent nonproductive cough, dyspnea, pleuritic chest pain, malaise hemoptysis, and fever [12]. The manifestations of COP are usually so suggestive of infection that most patients receive at least one failed antibiotic treatment at the time of making a confirmed diagnosis [13]. Clinical examination commonly demonstrates inspiratory crackles (Velcro crackles). Wheezing and cyanosis can be found but not common and rarely patients may have clubbing.

The clinical presentation of CT-ILD is variable, ranging from cough to pleuritic pain and progressive shortness of breath. CTD-ILD has a higher prevalence in female patients and individuals aged between 40 and 60years [14]. Most CTD-ILD are characterized by a dry cough and gradually progressive dyspnea and have a classifiable CTD at the time ILD is recognized. ILD may be the presenting feature in some patients that follows CTD, while in others the CTD symptoms predate ILD [6,8,15]. Symptoms of CTDs including arthralgia, morning stiffness, skin rash, dry eyes, dry mouth, Raynaud's phenomenon, proximal muscle weakness, and muscle pain that are also common in CTD-ILD patients depending on the type of underlying CTD. Face swelling and oral ulceration are present but rare. The two most frequent physical findings include tachypnea at rest and

inspiratory crackles. Other signs like joint deformity, joint stiffness, skin rashes, skin thickening, etc are present depending on the underlying CTD.

Laboratory findings:

Blood tests are not diagnostic in COP. The white blood cell count, C-reactive protein level, and erythrocyte sedimentation rate are moderately elevated in most patients[16,17,18].

Anemia is the most common finding in CTD, due to autoimmune hemolysis in most conditions. Patients with CTD-ILD also have lower levels of erythrocyte, and hematocrit but high levels of platelet and IgM in their serologic tests, but most of these parameters are within normal limits [19,20,21].

Anti-nuclear antibodies (ANA) are found in the majority of SSc patients. Antibodies against topoisomerase (ATA or anti Scl-70), anticentromere antibodies (ACA) and anti-RNA polymerase III (ARA) are the three main autoantibodies of which ATA antibodies are strongly associated with ILD[22]. Rheumatoid factor and anti-CCP antibodies predict the development of RA and have been described as the sole sign of underlying connective tissue disease in patients with isolated ILD[23]. In PM/DM, antibodies against aminoacyl-tRNA synthetases (anti-synthetases) have been strongly linked to ILD and anti-Jo1 is the most common anti-synthetase associated with ILD. Other known anti-synthetase antibodies include anti-PL-7, anti-PL-12, anti-OJ, anti-EJ, anti-KS and anti-Wa[24,25,26]. Sjögren's syndrome include ANA against ribonucleoproteins Ro/SSA and/or La/SSB which is mandatory for diagnosis. Other serological non-specific markers are polyclonal hypergammaglobulinemia, raised ESR and other non-SjS specific autoantibodies [27,28]. Autoantibodies are a hallmark of SLE and virtually all patients have ANA. Disease-specific antibodies include anti-double stranded DNA and anti-Sm,. Other SLE-associated antibodies, although not disease specific, include anti-Ro/SSA and anti-La/SSB [29,30].

Radiographic findings:

The most common finding in COP on plain chest X-ray include unilateral or bilateral patchy consolidated areas which are usually peripheral, subpleural or peribronchovascular [31,32]. High resolution Computed tomography (HRCT) confirms the diagnosis. On chest HRCT, patchy airspace consolidation (present in 90% of patients), ground-glass opacities, small nodular opacities, thickening and dilation of bronchial wall are seen. The patchy opacities are common in the periphery of the lung, often in the lower lung zone. There may be a perilobular pattern with ill-defined linear opacities that are thicker than the thickened interlobular septa and have an arcade or polygonal appearance[33]. The reverse halo sign (atoll sign) is highly specific, although only seen in about 20% of patients with COP [34].

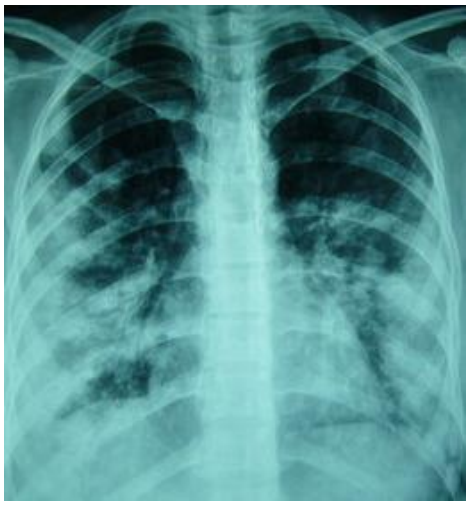

Figure 1: Chest X-ray of a COP patient that showing patchy densities in both lower lung fields, with blurred edges more in the peripheral lungs.

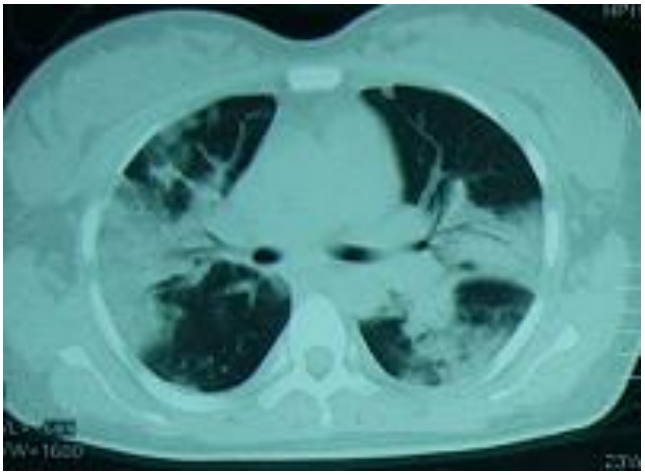

Figure 2: CT-scan with COP showing multiple patchy consolidations and strips around the pleura and bronchus

There are different patterns of parenchymal involvement in each CTD and there are significant overlaps. (Table 1) [35,36]. Overall, a radiographic non-specific interstitial pneumonia (NSIP) pattern is most commonly found in CTD-ILDs. It is characterized by intralobular and interlobular reticular opacities mostly in the subpleural and basilar area. Ground-glass opacities usually represent a higher degree of cellularity and suggest the disease is potentially more responsive to treatment, although not always true in some cases. Reticulation, traction bronchiectasis and honeycombing reflect more advanced ILD. Abnormalities in other thoracic structures (like esophageal or pulmonary artery dilatation with multi-compartment involvement) should raise suspicion for the presence of a CTD [37,38].

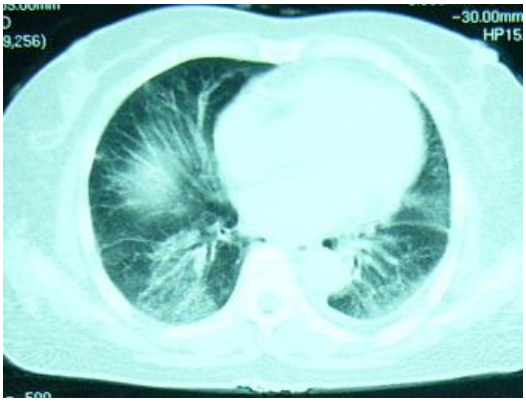

Figure 3: CT-scan of RA-ILD showing consolidation, ground glass opacity and striation of the lower lobes of both lungs.

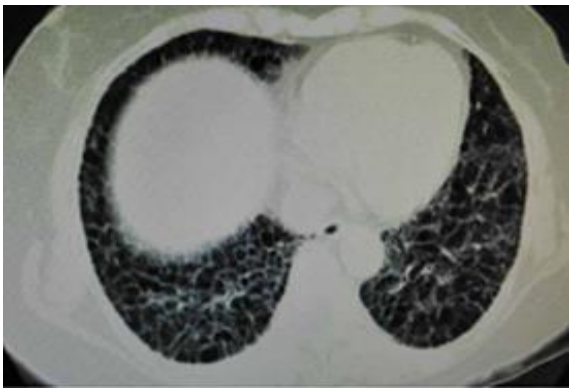

Figure 4: CT-Scan of SS-ILD showing ground glass opacities of lower lobe of both lungs.

Disease Association	Characteristic histological pattern	Characteristic radiographic finding on HRCT
Systemic sclerosis	Non-Specific interstitial pneumonia	Increased reticular marking, ground glass opacification, basilar prominence
	Usual interstitial pneumonia	Peripheral and bibasilar reticulonodular opacities with honeycombing
Rheumatoid arthritis	Usual interstitial pneumonia	Reticular changes and honeycombing
	Non-Specific interstitial pneumonia	Ground glass opacification with basilar prominence

Polymyositis/ dermatomyositis	Non-Specific interstitial pneumonia	As Above
	Usual interstitial pneumonia	As Above
	Diffuce Alveolar damage	Diffuse ground glass opacities
Sjögren's syndrome	Non-Specific interstitial pneumonia	As Above
	Lymphocytic interstitial pneumonia	Thin walled cysts, ground glass opacities, centrilobular nodules
Systemic lupus erythematosus	Acute Interstitial Pneumonia	Ground glass opacities
Mixed CTD	Non-Specific Interstitial Pneumonia	Septal thickening and ground glass opacities

Table 1: Charecterisitc histological pattern and radiographic finding on HRCT of different Connective tissue associated Interstitial Lung Disease.

Pulmonary function tests:

The PFT finding in COP patients in most cases is a mild to moderate restrictive ventilatory pattern and decreased diffusion capacity, although, an obstructive pattern may be observed in smokers [39].

The interpretation of lung function in the context of CTDs can be complex depending on the various of CTD diseases associated. In general, most of the CT-ILD show a restrictive pattern, with proportional reduction in FVC and forced expiratory volume in the first second (FEV1), and concomitant reduction in the transfer coefficient for carbon monoxide (DLCO). However, clinicians should be aware that a different PFT-abnormalities can occur when other thoracic components such as airways, vasculature or chest wall are involved (as may occur in CTD) [40].

Lung Biopsy:

Although rarely done, lung biopsy in COP shows excessive granulation tissue proliferation within small airways and alveolar ducts, with chronic inflammation in the surrounding alveoli.

In CTD-ILD patients, the non-specific interstitial pneumonia pattern of lung injury is most common except for RA, in which usual interstitial pneumonia-pattern pathology is more common [41].

Treatment and Prognosis:

Corticosteroids have been widely used for the treatment of COP and most patients recover completely with good prognosis although recurrence might develop especially while decreasing the dose of corticosteroids

or stopping treatment [42,43]. The regression of symptoms and radiological improvement are usually observed within a few days. Treatment is normally continued at for 2 to 4 weeks and then discontinued at 6 to12 months by gradually decreasing the dose according to the response [44,45].

Not all patients with CTD-ILD require treatment. The decision to initiate treatment in CTD-ILD depends on severity of lung function abnormalities and likelihood of ILD progression since immunomodulatory medications are associated with significant adverse effects [46,47]. CTD-ILD is often have a good response to immunosuppression. In the presence of significant ILD, treatment options include corticosteroids in all CTD except for SSc (risk of renal crisis), often in combination with an oral immunosuppressant from the start [48]. The most commonly used oral immunosuppressant is Azathioprine in CTD-ILD.

In the case of severe, and/or rapidly progressive ILD especially with high chances of progression and significant mortality, high-dose corticosteroids along with or without intravenous cyclophosphamide are administered in order to gain control of the disease rapidly [48]. The prognosis of CTD-ILD is better than many other subtypes of ILD given that the treatment is started early with an approximately 70% 5-year survival although recurrence is also common especially during adjustment of doses and stopping treatment may lead to relapse [49].

CONCLUSION

From this review, we can notice that the clinical manifestations of COP and CTD-ILD and mode of treatment are not the same but COP and CT-ILD both have a relatively better overall prognosis than other types of ILD. However, the response rate of COP is better compared with CTD-ILD with less recurrences and relapses. A study can be conducted to analyze and compare between the two subtypes of ILD.

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