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A Review on Interstitial Lung Disease Associated With Rheumatoid Arthritis

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ABSTRACT

Interstitial lung disease is a condition that causes gradual scarring of the lung tissue. This may be due to some chemical exposure or even due to substances like coal and asbestos dust. It may also tesult from auto immune conditions such as rheumatoid arthritis. The scarring which occurs in this condition is usually irreversible. The common symptoms of this condition includes dry cough and SOB on exertion. The diagnostic procedures include HRCT chest imaging, blood tests, bronchoscopy, bronchoalveolar lavage , pulmonary function tests and rarely surgical biopsy. The basic first line therapy includes corticosteroids, DMARDs based on the condition and type of ILD in the individual patient followed by a lung transplant if needed.

Key words:
Interstitial Lung Disease,
HRCT Chest Imaging,
Disease Modifying Anti Rheumatic Drugs (DMARDs)

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INTRODUCTION:

Rheumatoid Arthritis is a chronic systemic inflammatory condition potrayed as dynamic progressive devastation that occur to joints in the body. RA affects approximately 1% of the population and it is expected that 20 lakh young adults in the US are troubled by this condition. Women are three times more likely to be affected than men[1]. The cause of the disease remains unclear . A lot of immunological occurance are recognised ,a lot of which are used for targeted delivery of drugs [2].The criteria for diagnosis given by the American Rheumatism Association is as follows

- stiffness of bones in the early hours
- inflammation and deformation of more than two joint regions
- inflammation & deformation of proximal interphalengeal, metacarpal phalengeal joints.
- Symmetrical arthritis
- Nodules associated with RA
- Presence of rheumatoid factor[3].

However joint problems are the main appearance in RA, it has other conditions like extra-articular indicators that lead to the significant illness and increased death observed with this disease. Although heart conditions are one of the cause for most RA-related mortality, lung disease also plays a maximum role, leading nearly about 10% to 20% of all deaths. lung problems transpire in almost 60% to 80% of people suffering with RA, in them most of them are without any symptoms. RA directly affects all internal parts of the thorax, including the lung parenchyma, large and small airways, pleura, and to little extent the vasculature. In addition, lung infections due to pathogens and lung disease caused with immunosuppressive agents like DMARDS and biologic agents used for the treatment of RA cause drug induced lung disorders. RA-associated lung disease naturally occurs within 5 years of RA diagnosis and sometimes lead to joint diseases in up to 20% patients[4]. In this review we focus on pulmonary expressions of rheumatoid arthritis, clinical manifestations, Pathophysiology, diagnosis, RA drugs inducing ILD and treatment.

PULMONARY EXPRESSIONS OF RHEUMATOID ARTHRITIS:

1. Interstitial lung disease
   - Organising pneumonia
   - Usual interstitial pneumonia
   - Nonspecific interstitial pneumonia
   - Acute interstitial pneumonia
   - Lymphocytic interstitial pneumonia
2. Airway disease
   - Bronchiectasis
   - Cricoarytenoid arthritis
   - Constrictive bronchiolitis
   - Follicular bronchiolitis
3. Rheumatoid nodules
4. Pleural disease
   - Empyema
   - Pneumothorax
   - Pleural effusion
   - Pleuritis
5. Vascular disease
   - Vasculitis
   - Pulmonary hypertension
6. Drug toxicity
7. Fibrobullous disease
8. Rheumatoid pneumoconiosis
9. Amyloidosis Infection[5].

RHEUMATOID ARTHRITIS INDUCED INTERSTITIAL LUNG DISEASE:

Atopsy studies suggest that pulmonary manifestations are the 2nd most common cause of death due to RA ,the first being infection [6]. Pulmonary manifestations are found in late course of this disease because they appear in the sub –clinical phase and the patient is primarily limited to articular disease[7].ILD is the most common symptomatic pulmonary manifestation of RA. It occurs most commonly in men than in women, particularly with respect to a high RF titre and end stage joint disease. Radiographically, ILD associated with RA is indistinguishable from pulmonary fibrosis (IPF) of unknown cause and ILD that occurs together with other connective tissue diseases[8,9]. The classification of ILD based on the histopathology of the condition is given by The 2013 American Thoracic society and European Respiratory Society [10]. The various forms of ILD that occurs with RA are

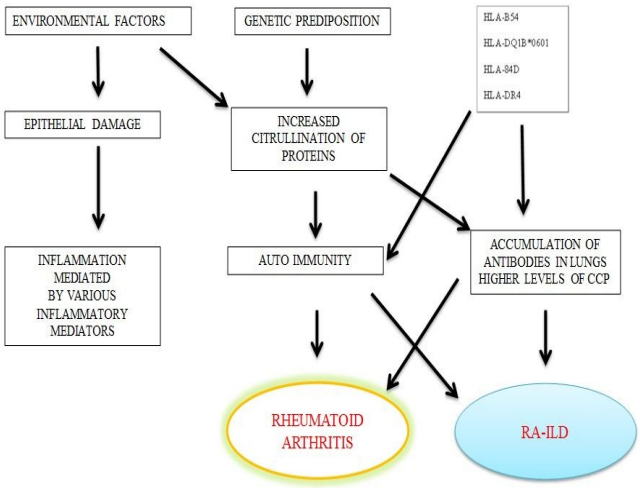
- Usual interstitial pneumonia (UIP)
- Non specific interstitial pneumonia (NSIP)
- Organising pneumonia (OP)
- Desquamate interstitial pneumonia
- Alveolar damage[11, 12].

RA THERAPY INDUCED ILD:

- METHOTREXATE : Methotrexate has a serious side effect of mucosal ulceration leading to necrosis in the lung tissue.
  indications of dyspnea, cough and fever [13].
  Radiological patterns: common findings like interstitial granulomatous infiltrates with ground glass opacification on chest CT [14]. Unusual findings like, pleural effusions, reticulonodular disease, hilar lymphadenopathy [15-18].
  Incidence : 0.3-11.6% [19].
- ANTI TNF (adalimumab, certolizumab, gilomumab, infliximab, etanercept) drugs produces indications of dyspnea.
  Radiological findings include aseptic pulmonary nodules which are granulomatous, both necrotising and non necrotising [20, 21].
  Incidence: 0.5-3% [22].
- LEFLUNAMIDE increased t-cell activation caused by leflunamide leads to pulmonary fibrosis. It produces indications of dyspnea, fever, cough [23].
  Radiological findings: diffuse or patchy ground glass opacities, usually with septal thickenings[24]. Incidence: 1%[23].
- RITUXIMAB was primarily used in leukaemia. Later in 2006 it was approved by EMEA for arthritis. Literature reviews suggest that administration of rituximab causes lung disorders in patients who are administered with anti rheumatoid arthritis drugs mainly DMARDs. It produces indications of dyspnea.
  Radiological findings: acute or subacute OP [25], acute respiratory distress [25].
- SULFASALAZINE has an unknown mechanism in inducing ILD. However one of the adverse effects of salfasalazine was found to be pulmonary toxixity.
  It produces dyspnea and cough. Radiological findings: esinophilic pneumonia and peripheral esinophilia[26].

PATHOPHYSIOLOGY:

Rheumatoid arthritis is a condition caused due to buildup of excessive citrullinated proteins in the synovial area. Interstitial Lung Disease (ILD) is a condition caused due to extreme curative effect in response to injury of lung ensuing fibrosis of lung. RA-ILD is a resultant reaction of extreme curative effect in healing the damage caused by excessive diposition of citrullinated proteins.



CLINICAL MANIFESTATIONS:

The indications of ILD commonly arise after the attack of arthritis, 1/5th of patients with lung predates articular disease [27]. Patients sometimes may found to be without any symptoms , but the common observed complaints are shortness of breath and cough[28]. Lung fibrosis, finger clubbing are commonly observed and are seen in almost 75% of cases[27], although not as commonly as in idiopathic lung fibrosis [29]. Generally, ILD related with RA have a tendency to follow a short course than the idiopathic form of a disease. Sometimes patients may advance to respiratory failure of end stage[30].

The symptoms that occur generally develop in the time course; however, the rate of this development differs from affected person to person and among the diverse types of ILD. Literatures show that an IUP patient may develop symptoms faster than other types of ILD in RA[31, 32]. Hypertension in pulmonary artery (PAH) is majorly related with systemic sclerosis, developed in ILD with RA[33]. The indications of the atricular inflammation lead to the occurance of ILD in maximum number of cases [34].

DIAGNOSIS:

The identification of RA-ILD is based up on pulmonary function tests, HRCT and rarely lung biopsy[35]. A deep study on patient history including his occupation, environmental and pharmaceutical factors should be piloted to calculateprobablealternate cause.The most significant diagnoses are either related to previous or present infection and drug toxicity because of the therapy. The possibility of severe infection in persons with RA is 2x times greater than normal[36]. The pattern of radiographic anomalyobserved on HRCT in RA has showed to be an exceptional predictor of the basic pathologic outline. UIP, NSIP, and BOOP are strongly interrelated with the originalpathology[37, 38]. Inaddition to pathological patterns, radiographic patterns are also used for prediction of development and consequence in RA-ILD.

PULMONARY FUNCTION TESTS:

PFTs normally determine fall in lung volumes and DLCO, even in the asymptomatic stage[39].Reduced DLCO is the most apt marker for interstitial pneumonia on HRCT [40]. The sensitivity of x-rays for the identification of ILD is low (5-25%), when compared to HRCT, disclose signs of ILD in about 50% of patients suffering with RA41.

DIAGNOSTIC PATTERNS

- USUAL INTERSTITIAL PNEUMONIA with a prevalence of 44-66% shows areas of fibrosis and fibroblastic foci in the histological pattern. It appears as bilateral basal and sub pleural reticulation on radiological pattern.
- NON SPECIFIC INTERSTITIAL PNEUMONIA with a prevalence of 24-44% shows uniform cellular infiltrate and interstitial fibrosis; but lacks honeycombing in the histological pattern. It appears as prominent ground glass opacities with absence of honeycombing on radiological pattern.
- ACUTE INTERSTITIAL PNEUMONIA with a prevalence of 0-11% shows oedema with alveolar damage and hyaline membranes in the histological pattern. It appears as progressing ground glass changes with consolidation of base.
- CRYPTOGENIC ORGANISING PNEUMONIA with a prevalence of 0-11% shows interstitial inflammation, organization of alveolar ducts (rarely alveoli and bronchioles) in the lumen of lung tissue[42].

HOW TO DIAGONISE THE PATIENT FOR ILD WITH R.A:

- Firstly constitutional symptoms like swallowing difficulty, rashes, and joint pains causing physical discomfort, symptoms of sicca and raynaud phenomenon are the main elements of history.
- Secondly we should evaluate for papules, ulcers, and proximal muscle weakness in the physical examination.
- The laboratory tests should aim at evaluating rheumatoid factor which is anti cyclic citrullinated peptide.
- Total lung capacity, FVC should be evaluated on the basis of 6min walk distance and oxygen saturation in a pulmonary function test.
- All the suspected patients should take radiographic tests like HRCT scan and NSIP to see the unusual patterns of RA –ILD.
- Pathologically the biopsy of lung specimen shows unclear biopsy samples from upper middle lower lung fields[43].

TREATMENT FOR RA-ILD:

Drugs used in treatment of interstitial lung disease are:

- PREDNISOLONE with a dose of 0.5-1mg/kg/day upto 60mg/day
- METHYLPREDNISOLONE with a dose of 1g/day IV for 3 days
- AZATHIOPRINE with a dose of 1-2mg/kg/day
- CYCLOPHOSPHOMIDE with a dose of 1-2mg/kg/day PO or 500-1000mg IV pulse every 4 weeks
- MYCOPHENOLATE MOFETIL with a dose of 1-1.5g bid

The basic therapy for newly identified RA-ILD is a dose of prednisone which is higher than the original dose [45]. Immunosuppressive agents are not usually used. New agents like mycophenolate[46], rituximab and tocilizumab[47]. Mycophenolate with a dose of 1-2mg a day in persons with mild condition has reported to alleviate RA-ILD, although it does not always appear to be active in improving the articular indications of the disease, for this condition we use disease modifying anti rheumatic drugs[48]. The safe and efficious use of Rituximab in treating RA induced ILD is presently under investigation. Imatinib a tyrosine-kinase inhibitor used in treating of chronic myeloid leukemia has also been recommended in the treatmentof RA induced ILD[49]. A recent finding shows the efficacy when given along with cyclophosphamide in the treatment of ILD[50].Tocilizumab is a humanized antihuman IL-6 receptor monoclonalantibody possiblyalter the process of ILD and other systemicindications of RA since IL-6 is majorly expressed on cells in rheumatoid synovial tissue[51] and it is also observed to have increased correlation with various factors of disease activity[52, 53].

Drug induced pneumonitis also should be taken in account when diagnosis of RA-ILD. Cyclophosphamide at a dose 10–15 mg/kg is generally given in IV route along with methylprednisolone at a dose 7–10 mg/kg at every third week for six doses in RA-ILD patients with high severity[48].At the end the medication, it is necessary to check the lung function. Responders are commonly given with less dose of prednisone PO and azathioprine PO at a dose1–2 mg/kg to maintain the therapeutic action, often on an undefined basis[53].

SUMMARY:

RA-ILD is the most projecting and devastating indication of Rather is many factors that can vague the diagnosis, but rapid diagnosis and treatment may delay the development to last stage lung disease. Unlike, once RA-ILD had been identified, it is often, challenging for the clinician assessment procedure. Is it the disease, the drugs or some other distinct factors backing the weakening in lung function. We can make early diagnosis with the advent of recent advancements in HRCT along with supporting clinical and physiological data even in patients without symptoms. Respiratory tract infections are commonly found in patients who are under treatment of DMARD'S and biologics, so it is very important to check for the symptoms like dyspnoea, cough in such patients to have a control over the progression of disease. Alter all the testing procedures and after a clear final diagnosis is made, the treatment plan should aim at the symptomatic relief and also slowing down the progression of the disease. This review also brings awareness about ILD which is a very common effect due to administration of drugs used for RA.

CONCLUSION:

Pulmonary manifestations are the most common complications of rheumatoid arthritis. Of which interstitial lung disease is an important manifestation and is most commonly seen in majority of the patients with rheumatoid arthritis. RA-ILD is also caused by the drugs used in RA therapy. Prednisolone, methyl prednisolone, azathioprine, cyclophosphamide, mycophenolate mofetil are the drugs used in the treatment of RA-ILD based on individualized treatment.

DIAGNOSTIC ALGORITHM FOR EVALUATION OF RA:

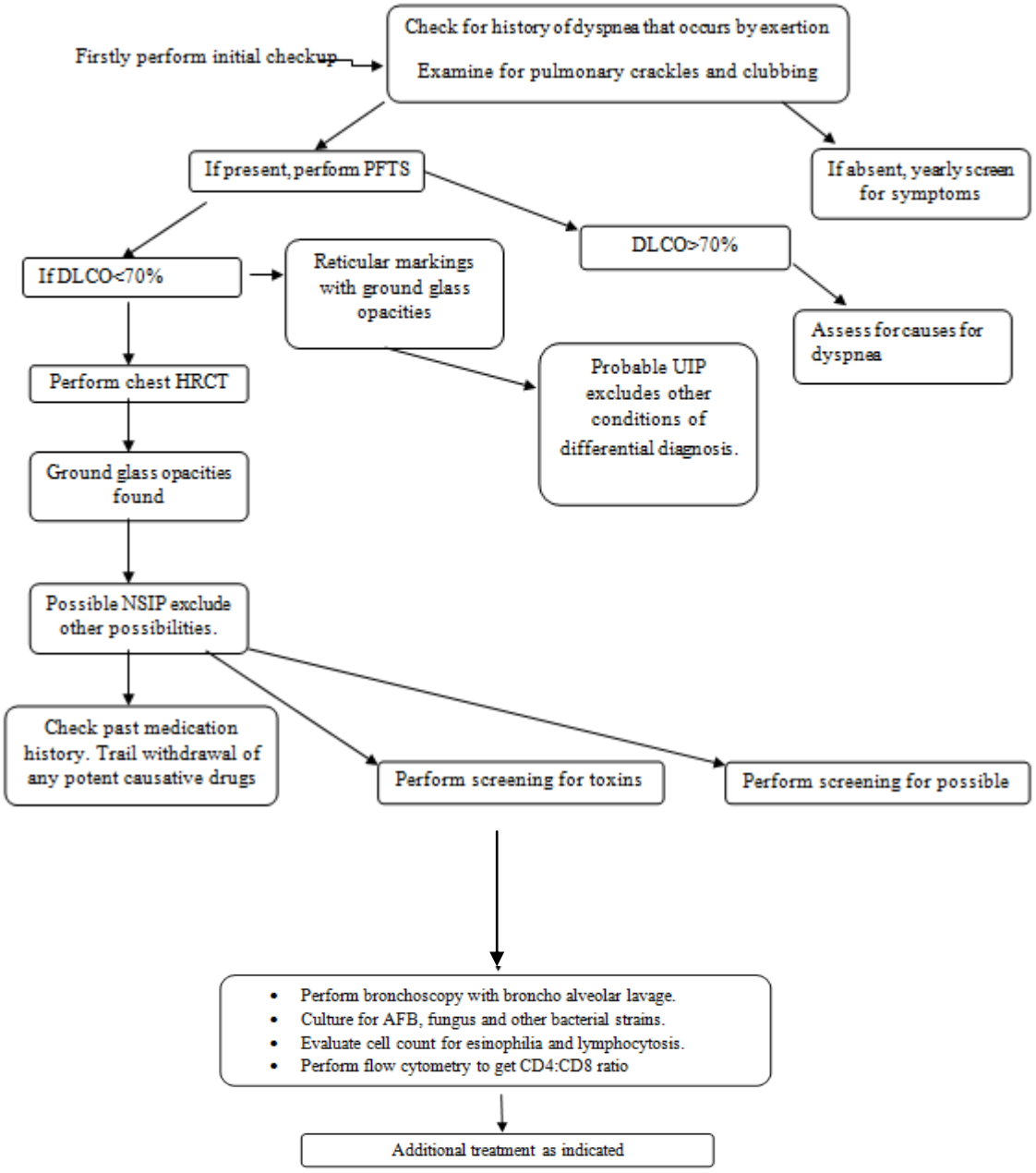


Fig1: Diagnostic algorithm for the evaluation of rheumatoid arthritis[44].

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