INTERSTITIAL LUNG DISEASE IN PATIENTS WITH RHEUMATOID ARTHRITIS – FACTS AND PERSPECTIVE

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Abstract

Rheumatoid arthritis is the most common form of systemic autoimmune disease. It predominantly affects joints and synovial tissues, but there are also significant interstitial changes. More often in recent years there are patient cases of rheumatoid arthritis complicated by interstitial lung disease. It is questionable whether this pathology is the result of natural disease progression or is rather the side-effect of used medication. For the latter, there is general concern for the long-term use of Methotrexate. However, research carried out in a number of international research centers shows inhomogeneous data. Another point of consideration is which biomarkers should be used to follow-up patients and which risk factors can determine the population at risk of developing interstitial lung disease. Answering these questions would help adjust the therapy and mitigate the risk of developing this complication. Recently, the use of anti-fibrotic drugs as part of the treatment plan is being discussed, along with the need to separately determine joint and lung status of the patient. Currently, there are no existing, approved protocols for treatment of rheumatoid arthritis complicated with interstitial lung disease.

Keywords: *rheumatoid arthritis, interstitial lung disease, Methotrexate, pathogenesis*

Introduction

Rheumatoid Arthritis (RA) is the most commonly met form of inflammatory connective-tissue disease in the world. While predominantly we associate rheumatoid arthritis with skeleton-muscular affliction - affecting one or multiple joints with well-known signs of inflammation and erosion - it is vital to recognize the visceral changes, developing over time. Most notably the lungs and the heart are targeted by this systemic disease. Out of all the visceral manifestations, interstitial lung disease (ILD) seems to have the most significant prognostic effect for patients. In this review, we shall focus on discussing exactly ILD in terms of it being the most severe complication in patients with RA for which to this day there is no clear treatment strategy.

The diagnosis

By definition, interstitial lung disease is a heterogeneous group of parenchymal lung diseases that are characterized by diffused parenchymal inflammation and fibrosis - both present in the connective tissue of the lung to a varying degree [1]. They mainly affect the peripheral lung interstitium of the alveolar walls. It is often found that small vessels and smaller airways are also afflicted in ILD. The representation of this lung complication in patients with rheumatoid arthritis is diverse due to some genetic factors, external factors, and the main disease activity - in this case, RA. The manifestation of interstitial lung disease is much feared by practitioners because it significantly increases both morbidity and mortality [2]. In diagnosing respiratory symptoms of patients with rheumatoid arthritis, the clinician must consider other possible differential diagnosis - chronic obstructive pulmonary disease (COPD), bronchiectasis, respiratory infections following immunosuppressive therapies, drug-induced pulmonary toxicity, and ischemic heart disease [3]. While interstitial lung disease has been diagnosed in patients with RA, it is often commonly found in other auto-immune and connective-tissue diseases such as Sjogren syndrome, scleroderma, and inflammatory myositis [4, 5, 6]. Despite its wide prevalence, little is known about the pathogenesis of ILD.

Epidemiology and significant risk factors

Clinically represented forms of interstitial lung disease associated with rheumatoid arthritis (RA-ILD) are found in 2% to 10% of all patients with RA [7]. However, we should note that this prevalence documented in different studies must be considered with caution due to the heterogeneous representation of ILD, the discussions around the actual definition of interstitial lung disease, and the different methods used to diagnose patients. Further research has established that the population at risk of developing ILD among the patients with RA is 6%-15% [8, 9]. In most cases, ILD is diagnosed after RA, as a complication of the latter. Clinical observations show that the longer the duration of the main disease, the greater the risk of developing complications including interstitial lung disease. Usually, ILD manifests within the first five years after diagnosing RA [11]. However, some research suggests that there are those cases where ILD is manifested years before the development of rheumatoid arthritis [10]. Over the years some risk factors for developing ILD have been named. These include older age and male gender [12], smoking [13], positive anti-cyclic citrullinated peptide antibodies (ACCP), IgM rheumatoid factor [14], and rheumatoid arthritis disease activity [10]. Smoking is the only preventable risk factor of all of the above-mentioned. When smoking is discovered as a risk factor in the patient's history, the practitioner should determine for how many years has the patient smoked and roughly how many cigarettes per day. It is worth noting that passive smokers are also at a greater risk of developing interstitial lung disease associated with rheumatoid arthritis. When diagnosing ILD in patients with RA it is key to look for risk factors related to the patient's occupation - the presence of dust, toxic substances, inhalation of chemicals, number of years the patient has been exposed to those, and other factors. The clinician should also focus their attention on determining risk factors in the living environment -

dust, smoke, soot, chemical substances, the burning of coal or other biofuels mostly for heating, but for other purposes, too. Again, if a risk factor is determined, the duration of the exposition should also be calculated. A significant discussion in terms of risk factors has surrounded the drugs used to treat RA. This is especially true about disease modifying drugs such as Methotrexate, Leflunomide, Azathioprine, TNF-inhibitors, etc. Extensively have been studied the effects of Methotrexate as one of the drugs that are mostly used in patients with rheumatoid arthritis to control disease activity and symptoms. Recent studies have shown that there is very week evidence to support the claim that the drug can cause ILD in patients with RA [15]. The research by Dawson et al. [15] has suggested that Methotrexate may be associated with some fibrosis in the lung's interstitium. Furthermore, that patients who had developed interstitial lung disease associated with rheumatoid arthritis and were then treated with Methotrexate had a better survival rate compared to those patients who were not given disease modifying drugs. While the median survival of patients with RA is 9.9 years, there is a dramatic decrease in those diagnosed with RA-ILD – the median survival rate drops to just 2.6 years [9].

Pathogenesis

As was already mentioned the pathogenesis of RA-ILD is not completely clear. A number of studies in the field suggest that the most likely explanation for the changes that occur in the lung's parenchyma is due to an autoimmune process. This is a much supported thesis since the development of pathological changes in general in patients with rheumatoid arthritis is due to an autoimmune process. ANCA, which are already proven to be a significant factor for the pathogenesis of RA, are also discussed in terms of ILD. This would also explain why smoking is a significant risk factor for the development of RA-ILD. In smokers, higher levels of ANCA have been established. But the evidence is not homogeneous. ILD in patients with rheumatoid arthritis does not develop in a manner similar to that in patients with other conditions, such as scleroderma. There ILD develops as a non-specific interstitial pneumonia, whereas in patients with RA the mechanism of ILD is like that of a usual interstitial pneumonia. It is paramount to distinguish between the two because, for one, the usual interstitial pneumonia has a much worse prognosis in comparison to non-specific interstitial pneumonia for which there is no available treatment. But also because of the duration of the primary condition. In patients who were recently diagnosed with rheumatoid arthritis, ILD develops as a non-specific interstitial pneumonia. However, with the progression of RA, ILD changes its pathogenetic mechanism and represents itself as a usual interstitial pneumonia [16]. Interesting to note is that smokers usually develop ILD by the mechanism of usual interstitial pneumonia, while non-smokers - by the mechanism of non-specific interstitial pneumonia. Once again this proves the significance of smoking as a risk factor for the development of RA-ILD. Some genetic hypotheses are discussed for the pathogenesis of RA-ILD. One such is the genetically determined α1-antitrypsin deficiency. It is a known factor in the development of COPD.

Clinical manifestation

The clinical representation of RA-ILD is varied. Patients may present with a cough, dyspnea, inspiratory wheezing, reduced lung volumes, restrictive changes in the lung function, lesser lung compliance, and abnormal x-ray imaging of the lung and chest. Broadly in ILD, there is vast fibrosis and loss of normal lung function [17].

Diagnosis

Imaging is a substantial part of diagnosing RA-ILD. X-ray which is usually the first choice in almost all lung diseases, in this case, shows no significant changes and cannot be widely used to detect interstitial changes [18]. HRCT is a mandatory part of diagnostics. The changes visible here are varied: ground glass-opacities, reticulation, consolidation, honeycombing, and nodules. HRCT can be used to determine whether there is non-specific or usual interstitial pneumonia [19]. Pulmonary function tests are also helpful though not always able to detect the changes. Research has shown that diffusing capacity of the lung for carbon monoxide (DLCO) is decreased. The changes established using pulmonary function test are airway obstruction, restriction, and decreased DLCO [20]. Many patients may present abnormalities on either HRCT or pulmonary function test but the majority will not have a significant clinical manifestation. Nevertheless, screening in patients with rheumatoid arthritis for ILD must remain a priority, especially should any respiratory symptoms occur. There is no officially established period between follow-ups. But in patients with no symptoms and no significant clinical activity 3-6 months is the recommended time frame between patient examinations.

Treatment

There are no protocols for the treatment of RA-ILD. Usually, treatment is only started once there is significant clinical manifestation. There is no evidence to support that starting the treatment before the development of symptoms can prevent the progression of interstitial lung disease. Treatment is much more effective in patients with non-specific interstitial pneumonia in comparison to those with usual interstitial pneumonia. As first line of therapy are used corticosteroids, Azathioprine, and Mycophenolate, while Rituximab or TNF-alpha inhibitors are reserved as alternatives. Treatment results are much better in patients with predominant inflammation and less effective in cases of lung fibrosis. Out of the clinical trials, Mycophenolate seems to be the most effective drug, even showing an improved lung function and in part restored lung volumes [21]. Antifibrotic drugs are being discussed as alternative options. Physiotherapy much improves the clinical symptoms, namely dyspnea and the walking distance. Smoking should be terminated to decrease the risk of disease progression. Vaccination should be done frequently since patients with RA-ILD are more susceptible to viral and bacterial infections, also in part due to treatment.

Conclusion

With the great number of patients in the world suffering from rheumatoid arthritis, the significance of interstitial lung disease as its main and most severe complication is rising. Furthermore, interstitial lung disease is a complication to several other prevalent connective-tissue and auto-immune diseases. Further studies into its pathogenesis and progression are necessary and are key to establishing a treatment protocol with high efficacy. Currently, there is no evidence-based treatment option for patients with RA-ILD. Immunosuppressive therapy is most widely used, but the side-effects can be significant. Ongoing research is looking into the potential positive effect of antifibrotic drugs.

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