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Rheumatoid Arthritis Interstitial Lung Disease

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1. Introduction

Rheumatoid arthritis (RA) is a systemic, autoimmune, inflammatory disorder affecting 0.5-1% of the North American population (Gabriel, 2001). It has a predilection for young women with an incidence rate of up to 130 per 100,000 compared with 70 per 100,000 in men [Minaur et al, 2004]. It is associated with a median survival decrease of up to 11 years compared to the general population (Minaur et al., 2004). The disease course may be complicated by extra-articular manifestations that confer an added burden of morbidity and mortality. RA-associated cardiovascular and infectious complications are commonly highlighted as major causes of morbidity and mortality in these patients (Maradit-Kremers et al., 2005). However, pulmonary involvement, the third leading extra-articular manifestation of RA, is now also recognized as a major cause of morbidity and mortality in RA patients. This was demonstrated in an autopsy study of 81 RA patients where the cause of death was determined to be infectious in 23.5%, cardiovascular in 17.3% and respiratory in 9.9% of patients (Suzuki et al., 1994). Pulmonary complications are the presenting manifestation of RA in up to 20% of patients (Brown, 2007). These complications include airway disease, pleural effusion, pulmonary nodules, and interstitial lung disease (ILD). This chapter will discuss the epidemiology, clinical features, management of RA-associated ILD (RA-ILD) and highlight the links between pulmonary involvement and autoimmunity.

2. RA-ILD

2.1 Scope and epidemiology

Reports of the prevalence of RA-ILD are widely variable and likely comprise significant underestimates owing to inconsistency of clinical criteria used to define the condition, methods used for disease detection, and heterogeneity of study populations. Identification of ILD is further confounded by the fact that many of the medications used for the treatment of RA have potential deleterious effects on the lungs. A recent population-based study from the Rochester Epidemiology Project suggested that as many as 1 in 10 patients with RA will be diagnosed with ILD over the course of the disease (Bongartz et al., 2010).

RA patients with extra-articular manifestations, in particular those with respiratory disease, are at increased mortality risk, with a standardized mortality ratio ranging from 2.5 to 5.0 (Brown, 2007). RA-ILD remains a major cause of death in RA; the median and 5-year survival is 3.5 years and between 37-39%, respectively (Hakala, 1988). The mortality risk was found to be most significant in the first 5 years after an initial hospitalization. In a more recent incident-based study from the Rochester cohort of 582 patients with RA, the risk of

death was found to be three times higher in RA patients with ILD compared to patients without ILD; the median survival following ILD diagnosis was only 2.6 years (Bongartz et al., 2010). In general, treating connective tissue disease-associated ILD (CTD-ILD) early, with immunosuppressive medications, not only may halt ILD progression, but may improve quality of life. This may be true for RA-ILD as well, but these disease-specific data are scarce. The poor prognosis of RA patients with ILD highlights the need for clinicians to recognize the clinical features of this condition and be cognizant of its course and management.

2.2 Clinical features and course

Clinical detection of ILD in RA patients may be challenging. The challenge stems from the non-specific clinical features of this condition and, typically, symptoms that are often masked or manifest in an insidious manner. Patients most commonly present complaining of worsening shortness of breath on exertion and a dry cough. Since this patient population suffers from arthritis that often limits their physical activity, the presentation of exertional dyspnea may in fact already denote advanced lung disease. Moreover, since maximum ventilation at peak exercise is approximately 70% of maximum voluntary ventilation (MVV), in the absence of significant lung disease, there is significant pulmonary reserve and exercise should not be limited by dyspnea (Hansen et al., 1984). Therefore, a low clinical threshold of suspicion should be maintained with respect to complaints of dyspnea in these patients. Complaints of lower-extremity swelling, syncopal episodes, and exertional chest pain may represent an underlying pulmonary arterial hypertension with right-sided heart failure, a severe complication of ILD. Clinicians should also be mindful of the fact that RA patients, particularly elderly patients, may have other co-morbid conditions such as congestive heart failure or anemia that may present with similar symptoms. Therefore, clinicians must consider and actively search for ILD in the presence of these symptoms, rather than simply assigning them to other more common co-morbidities.

Physical exam in early ILD may be normal. A small proportion of patients may have digital clubbing (Rajasekaran et al., 2001). Most commonly, RA patients with ILD will have bilateral fine crackles heard best at the end of inspiration and tend to be more prominent at the lung bases. Expiratory wheezing, bronchial or upper airway sounds are uncommon and their presence can suggest either airway disease involvement or a concomitant respiratory condition such as chronic obstructive pulmonary disease (COPD) or asthma. The presence of hypoxemia may denote a more advanced disease process. Physical exam findings of an elevated jugular venous pressure with CV waves, an abnormal hepatojugular reflux, and lower-extremity pitting edema can represent an underlying right ventricular dysfunction relating to pulmonary arterial hypertension. A parasternal heave, a prominent second heart sound, and a tricuspid regurgitation murmur on precordial exam, as well as a pulsatile liver and ascites on abdominal exam, are all findings suggestive of underlying advanced pulmonary arterial hypertension. Although uncommon in RA-ILD without concomitant COPD, clinicians should be aware of these physical findings to facilitate early detection of this serious complication.

Evolving evidence points to the existence of another unique clinical entity of RA-associated ILD in which patients also present with signs and symptoms suggestive of COPD. The syndrome of combined pulmonary fibrosis and emphysema (CPFE) was first described by Cottin et al. in 2005. CPFE was characterized by the association of tobacco smoking, significant dyspnea, impaired diffusion capacity on pulmonary function test, exertional hypoxemia and

radiological features of both emphysema and diffuse interstitial lung opacities. This clinical entity was also described in a retrospective study of 34 patients with a connective tissue disease (CTD), 18 of which had RA. This study demonstrated the presence of CPFE in patients with CTD, particularly RA, and identified several features that distinguish CPFE in patients with CTD compared to non-CTD CPFE (Cottin et al., 2011). These features include a female predilection, younger age, higher lung volumes but a lower diffusion capacity. Smoking was identified in the majority of CTD patients with CPFE, but not in all. The presence of these features led the authors to suggest that CPFE is a unique pulmonary manifestation in patients with CTD, particularly RA (Cottin et al., 2011). Therefore, when assessing RA patients with respiratory complaints, clinicians should inquire about tobacco smoking history and be cognizant of CPFE features as these patients would potentially need additional monitoring and screening for development of pulmonary hypertension.

RA-associated ILD is a chronic, progressive pulmonary manifestation that confers significant morbidity and mortality (see section 2.1). As will be described in the next section, RA-associated ILD is heterogeneous in its presentation, but can be further defined by its histologic features. The course, radiographic pattern, response to treatment, and prognosis of RA-ILD can be linked to the specific underlying histological pattern.

2.3 Histopathology

ILD is defined as varying levels of inflammation and fibrosis of the lung parenchyma (Cushley et al., 1999). The classification criteria for ILD has undergone revision over the past 10 years and is still evolving as there is increased awareness that different histopathologic subtypes correlate with specific clinical presentations and have differing prognostic and therapeutic consequences. Nevertheless, it is widely accepted that ILD associated with CTD constitutes a unique class within the spectrum of ILD. From histological perspective, virtually any of the known histological patterns of interstitial pneumonia (IP) can occur in association with CTD. However, certain histological patterns are known to be more commonly associated with certain subtypes of CTD. In the case of RA, the most common patterns identified are the usual interstitial pneumonia (UIP) followed by the non-specific interstitial pneumonia (NSIP) (Lee et al., 2005).

Infiltration of inflammatory cells (plasma cells, neutrophils, and different T cells subpopulations) as well as varying degrees of fibrosis of the alveolar wall can be found in both NSIP and UIP (Parra et al., 2007). The key differentiating histological feature between the two is the temporal uniformity of the lesions seen in NSIP versus the temporal heterogeneity found in UIP. Temporal heterogeneity refers to the presence of varying degrees of inflammation and fibrosis within the same diseased lung. Therefore, in UIP, areas of normal lung are adjacent to areas of active inflammation. There are expanding areas of fibrosis with fibroblastic foci at the leading edges. These fibroblastic foci are rich in dense collagen and proliferating fibroblasts and are considered the hallmark lesions of UIP (Katzenstein & Myers., 1998). Another parenchymal lesion associated with UIP is formation of interconnected cystic spaces, called honeycombing, which indicates end stage fibrosis without evidence of active inflammation. In contrast, lung tissue in NSIP typically shows a homogeneous pattern of lymphocytic infiltrates in the alveolar septae (Parra et al., 2007). These correspond with areas of ground glass attenuation on thoracic high-resolution computed tomography (HRCT) and are the most characteristic feature of NSIP (Katzenstein & Fiorelli., 1994, Travis et al., 2000).

RA-ILD can also infrequently present with acute interstitial pneumonia (AIP), a sub-acute to rapidly progressive respiratory failure, and diffuse alveolar damage (DAD). DAD is the histologic abnormality observed in the acute respiratory distress syndrome (ARDS), which may be triggered most commonly by lung infections, sepsis, drug-induced lung disease, and inhalational lung injury (Katzenstein et al., 1986). The term AIP is reserved for cases where the inciting factor is unknown. Histologically, DAD is characterized by diffuse distribution of a temporally homogeneous appearance with alveolar septal thickening and fibrosis including hyaline membrane formation (Katzenstein et al., 1986). Distinguishing AIP from DAD superimposed on a pre-existing ILD, such as UIP, can be technically challenging. Clinically, the histological findings of AIP confer a mortality risk exceeding 50%, typically within several months of diagnosis (Katzenstein et al., 1986; Parambil et al., 2006). Patients surviving the acute syndrome are commonly left with significant morbidity and are at risk of recurrences (Bouros et al., 2000; Vourlekis et al., 2000).

Finally, in addition to a vigilant search for possible infectious triggers, clinicians assessing RA patients with respiratory symptoms should also obtain detailed medication history as certain medications used for the treatment of RA, such as methotrexate, cyclophosphamide, sulfasalazine, and TNF-alpha inhibitors have potential pneumotoxic effects and can present with diffuse lung disease. These medications can lead to ILD, particularly the NSIP pattern, but also may lead to a histologic pattern known as hypersensitivity pneumonitis (HP); thus, the etiology of ILD in RA can present a challenge to clinicians. Careful history regarding the temporal relationship between initiation of drugs and onset of respiratory symptoms may be helpful in deciphering causality. Onset of pulmonary findings within a 2 month period of drug initiation and stability in lung function and/or radiologic damage upon discontinuation of the toxic culprit are findings that support a drug-related etiology of ILD (Dixon et al., 2010).

As an example, methotrexate, the most commonly used drug for the treatment of RA, can result in interstitial pneumonitis and pulmonary fibrosis at any time or dosage during the course of treatment (Hilliquin et al., 1996; St Clair et al., 1985; Swierkot & Szechiński 2006). And, while the clinical presentation may be identical to RA-ILD, methotrexate-related toxicity usually occurs within 6 months of initiation, often within 2-3 months, and does not involve progressive decline in pulmonary function test (PFT). Other clinical clues to methotrexate-induced ILD are fever and eosinophilia from serum or from bronchoalveolar lavage fluid. The histopathologic correlate of methotrexate-induced ILD may be one of HP, DAD or a cellular NSIP type pattern (Imokawa et al., 2000; Kremer et al., 1997; St Clair et al., 1985). In contrast, cyclophosphamide, another agent used for the treatment of RA, is usually associated with an insidious onset of pulmonary symptoms and typically occurs after prolonged use (Segura et al., 2001). Therefore, it is essential to be vigilant regarding pulmonary symptoms even among patients with stable treatment and those with established disease.

2.4 Evaluation and radiographic findings

The diagnostic gold standard for identification and classification of RA-ILD has traditionally been a surgical, open-lung biopsy. Yet, since chest imaging now has a good correlation with histopathology, such a biopsy is not always necessary for diagnosis (Yoshinouchi et al., 2005). In fact, chest imaging is now considered a critical diagnostic and prognostic modality when assessing patients with suspected RA-ILD. It is foreseeable that in the future, a composite of

radiologic and histologic data may be used to predict outcomes as it relates to RA-ILD, as this composite measure is now used in idiopathic pulmonary fibrosis (Raghu et al., 2011).

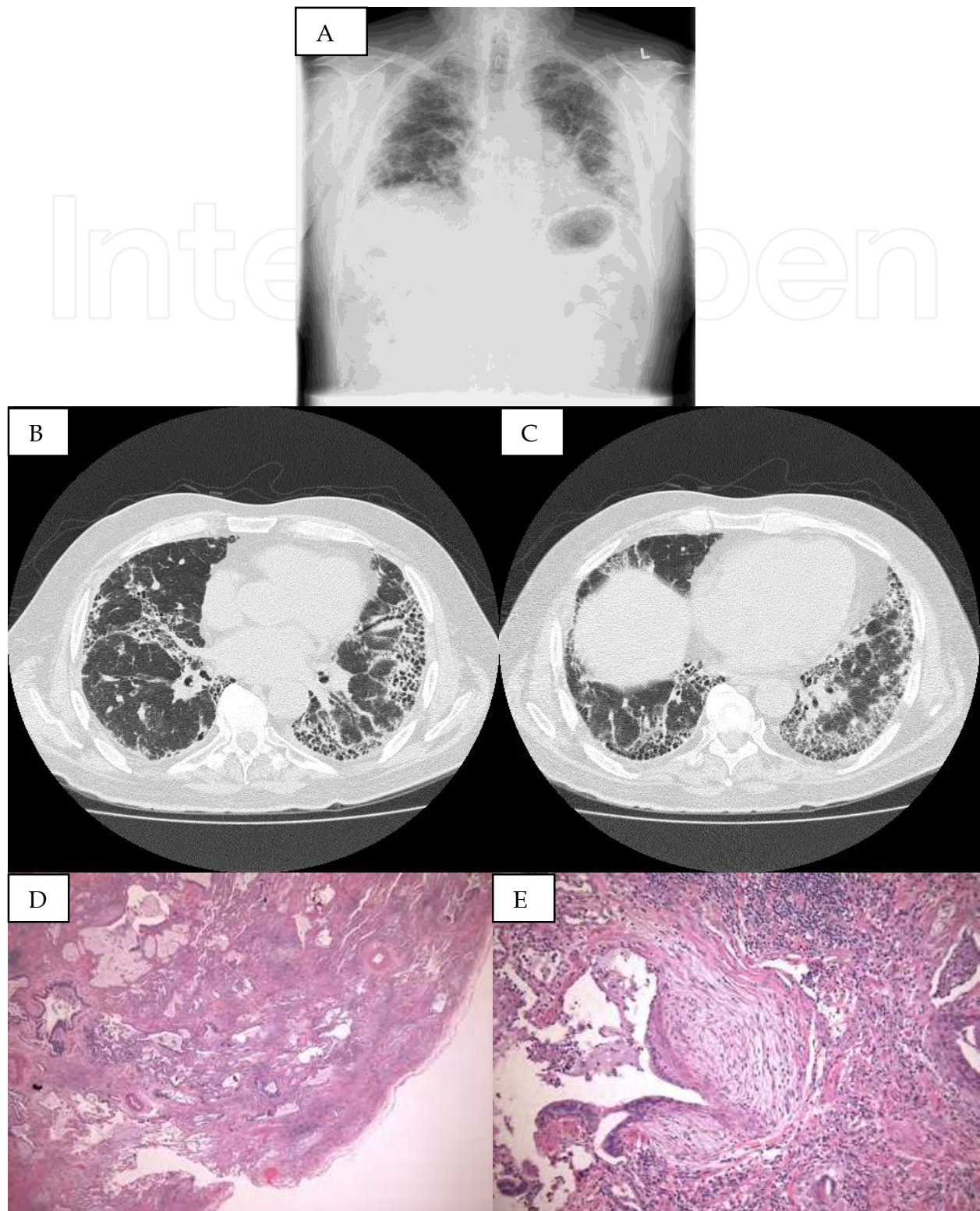
The chest radiographic pattern may be a useful screening test in select cases (Gabbay et al., 1997). Chest radiograph findings consist of a bilateral, peripheral, reticular opacity pattern with basal predominance. It is not possible to reliably distinguish between UIP and NSIP on chest radiograph. It is critical to recognize that patients with clinically important RA-ILD may have a completely normal chest radiograph; thus, the sensitivity of this test is inadequate to rule out RA-ILD. Instead, the standard of care in assessing patients with suspected RA-ILD is a thoracic high-resolution CT (HRCT), a method which has a very high sensitivity and can detect even mild disease.

HRCT provides a non-invasive radiological characterization of lung abnormality that may correlate reasonably well to the underlying pathology (Lee et al., 2005; MacDonald et al., 2001; Yoshinouchi et al., 2005). The characteristic UIP pattern on HRCT demonstrates marked interlobular septal thickening and intra-lobular reticulation, traction bronchiectasis (tethering open of otherwise relatively normal airways by the increased elasticity of surrounding lung) and honeycomb cysts, in a peripheral and basilar distribution (Macdonald et al., 2001; Martinez 2006) (See Figure 1). 'Ground-glass' opacities may be seen, but are atypical and the extent of ground glass and other atypical findings (such as upper lobe or central involvement) reduce the confidence that the radiologic pattern represents UIP (Macdonald et al., 2001, Martinez 2006).

In contrast to UIP, NSIP usually features more prominent 'ground-glass' changes. The 'ground-glass' changes tend to be symmetric with a basal and sub-pleural predilection. About half of all patients with NSIP will also have significant reticulation and a minority will have honeycombing (Yoshinouchi et al., 2005). Reticulation and honeycombing, when present in NSIP, are usually associated with the fibrosing sub-type (fibrosing NSIP) rather than the cellular sub-type (cellular NSIP) (See figures 2 & 3). The distinction refers to the histologic appearance of the lung interstitium, where the former is associated with more collagen deposition and the latter with more mononuclear inflammatory cellular infiltration. The distinction between UIP and NSIP on HRCT remains challenging in many cases, as demonstrated by a study of 50 patients with idiopathic ILD, where the HRCT pattern of NSIP was indistinguishable from UIP in 32% of patients (Hartman et al., 2000). The HRCT diagnosis of NSIP was found to have a sensitivity and specificity ranging from 60 to 70% (Hartman et al., 2000). The most distinguishing feature appeared to be the finding of more prominent 'ground-glass' changes in NSIP versus UIP (MacDonald et al., 2001). The radiographic appearance of AIP early in its course is quite distinct from UIP and NSIP, primarily by the presence of bilateral, frequently diffuse, airspace disease with air bronchograms. However, as AIP progresses, the airspace pattern becomes less prominent and instead it presents with 'ground glass' changes and reticular opacities, making the distinction between the various ILD patterns more difficult (Manjunatha et al., 2010). Overall, the diagnostic challenges using imaging modalities outlined so far highlight the underlying need of a more definitive tissue diagnosis by lung biopsy in select cases, which is further discussed in the next section.

2.5 Screening and diagnosis

The significant morbidity and mortality associated with ILD in RA patients calls for increased vigilance on the part of clinicians to respiratory complaints in these patients. Clinicians should inquire about the presence of any respiratory symptoms during both



A. Chest radiograph (PA view) shows bilateral, peripheral reticulation and volume loss, B&C. HRCT shows bilateral, peripheral reticulation, traction bronchiectasis and honeycombing, D. Surgical lung biopsy; low magnification (16x H&E) view of UIP with sub-pleural areas of microscopic honeycomb change interspersed with areas of less affected lung parenchyma, E. Surgical lung biopsy; high magnification (100x H&E) view showing a fibroblast focus likely representing active fibrosis.

Fig. 1. RA-ILD UIP

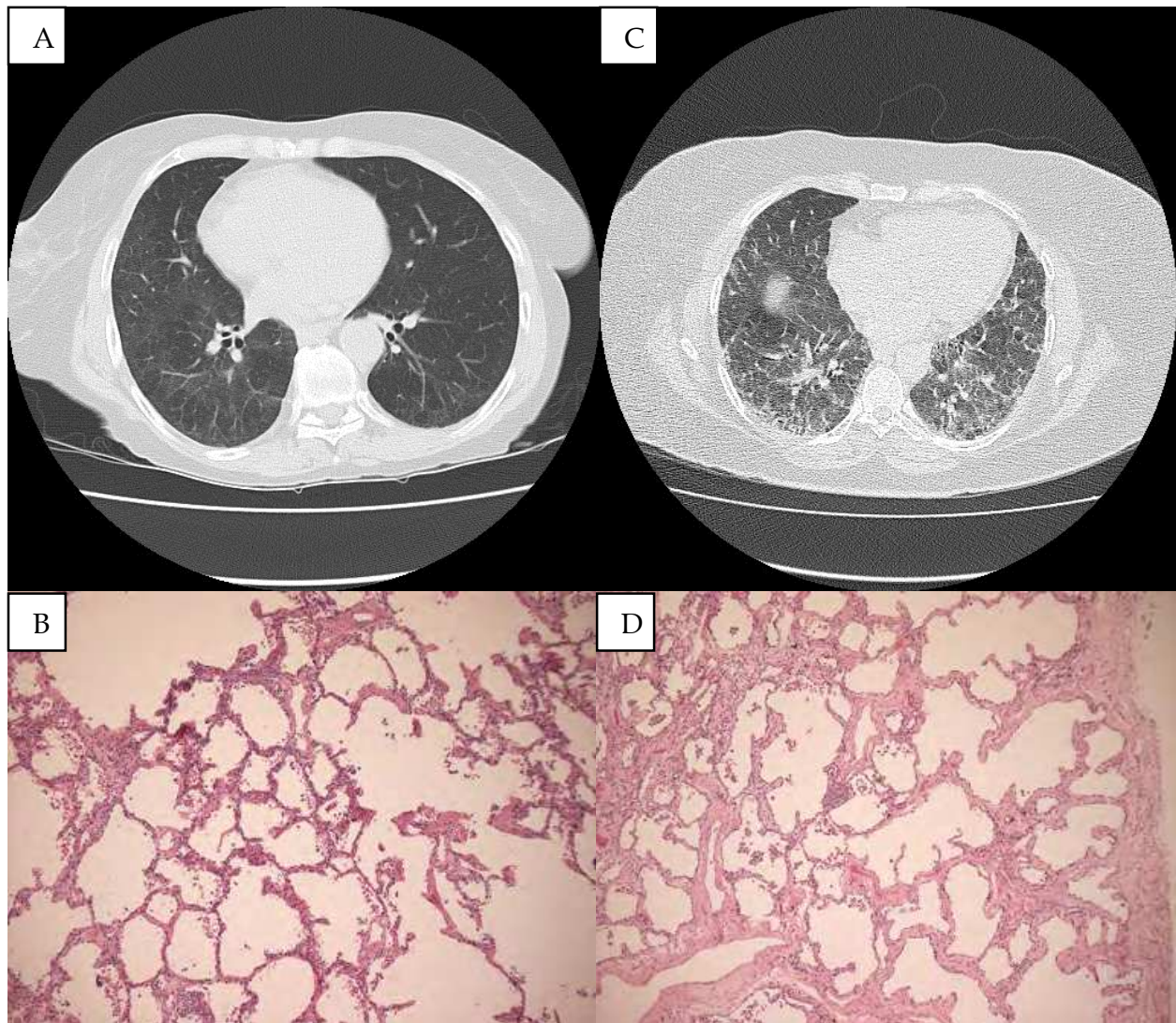
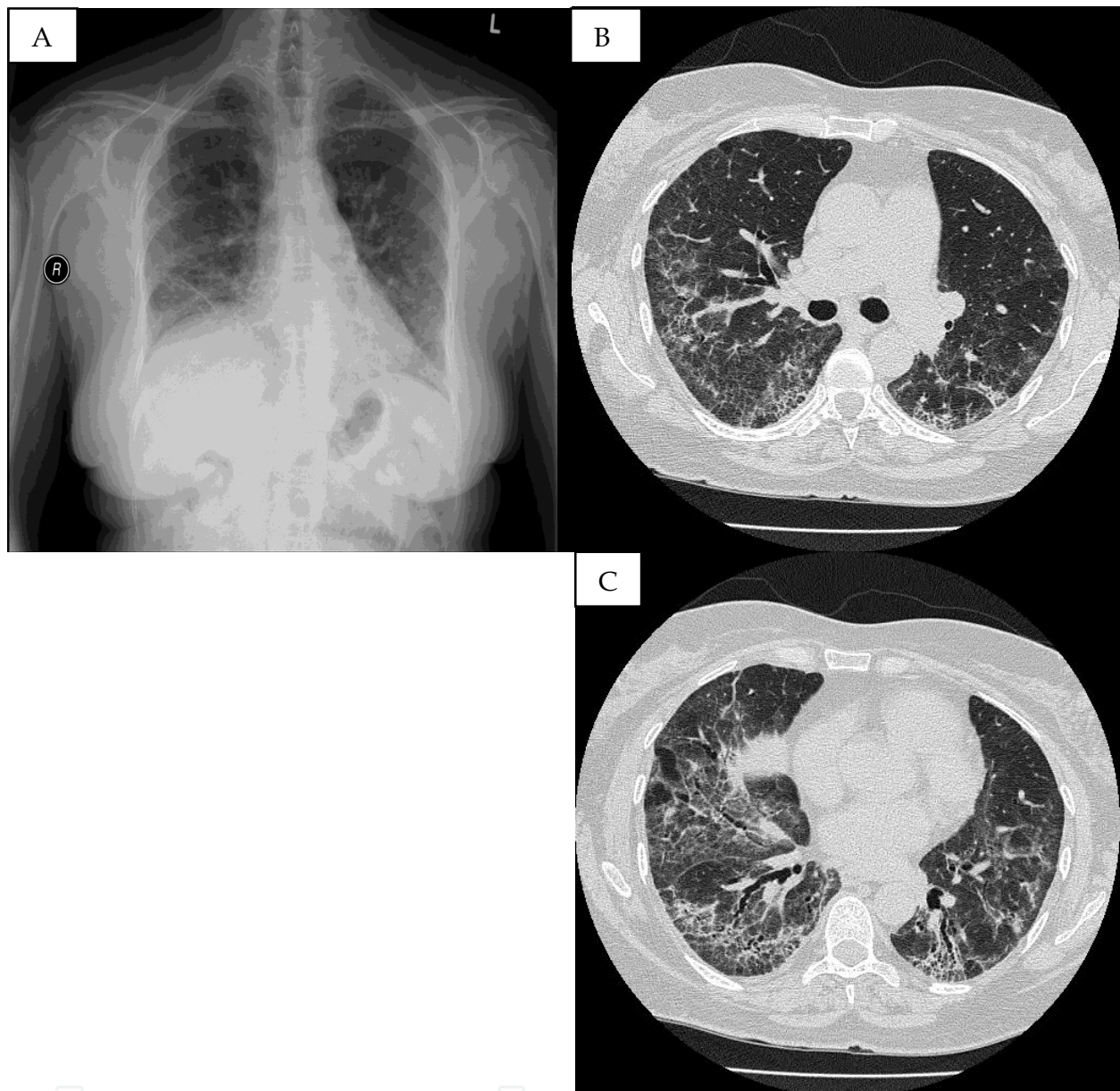


Fig. 2. A. HRCT of cellular NSIP in RA, showing predominantly peripheral and very subtle ground glass opacification, B. Surgical lung biopsy from patient in panel A; cellular NSIP with diffuse mild interstitial chronic inflammatory infiltrates (50x, H&E), C. HRCT of fibrotic NSIP in RA, showing predominantly reticulation, D. Surgical lung biopsy from patient in panel C; fibrotic NSIP with diffuse alveolar septal fibrosis without architectural distortion or remodeling (50x, H&E).

initial and follow-up visits, with particular emphasis on exertional dyspnea and persistent non-productive cough. Tobacco smoking history should be obtained from every RA patient and patients should be strongly encouraged to achieve smoking cessation and avoid passive (second-hand) smoking. A complete medication history should also be obtained to assess for any recent or current use of medications known to have potential pulmonary toxicity.

In the presence of respiratory symptoms, clinicians should also assess for any occupational or environmental exposures as well as for infectious stigmata. Examination of the respiratory system should be included in the routine follow-up of RA patients, with particular attention to the presence of bilateral inspiratory fine crackles as well as the less commonly encountered, inspiratory squeaks. In RA patients with known ILD, the physical examination should also include assessment for signs and symptoms of pulmonary hypertension.



A. Chest radiograph (PA view) showing peripheral interstitial markings, B&C. HRCT showing peripheral and lower lobe predominant ground glass opacification and reticulation.

Fig. 3. RA-ILD mixed cellular and fibrotic

It is standard of care that newly diagnosed patients with RA should complete a baseline screening chest radiograph, especially before the initiation of methotrexate. In most cases, particularly in patients with pulmonary risk factors such as smoking, or those who are symptomatic with dyspnea and/or cough, a baseline pulmonary function test (PFT), including spirometry, lung volumes and diffusion capacity, should also be completed. Although evidence-based, formal guidelines are not available, it is considered standard of care to also perform a chest radiograph prior to initiation of a biologic therapeutic agent, in part to evaluate for stigmata of latent or active tuberculosis, but also to assess for the presence of ILD which may be adversely impacted by the therapy (Dixon et al., 2010). In the absence of any lung abnormality at time of RA diagnosis, further investigations should be guided by clinical context, particularly in preparation for treatment with potentially

pneumotoxic medications. In the absence of specific evidence-based recommendations with regards to radiographic follow-up, clinical judgment should be exercised in making this decision.

Most commonly, ILD in RA is associated with PFT physiologic changes of restriction with a decreased diffusing capacity of carbon monoxide (Lee et al., 2005; Pappas et al., 2010). A decreased diffusing capacity is the most sensitive parameter for ILD on PFT. This may also be the sole PFT abnormality early in the course of ILD. A combination of obstructive and restrictive changes may co-exist in patients with other pulmonary co-morbidities such as asthma or COPD. As a result, some of these patients may present with combined obstructive and restrictive abnormalities or an isolated decreased diffusing capacity. For serial monitoring of PFTs, particular attention is paid to changes in absolute and percent predicted forced vital capacity (FVC) and diffusing capacity as markers of disease progression and response to treatment. A low diffusing capacity has been shown to be associated with disease progression and poor outcomes (Biederer et al., 2004, Hakala 1988). Less commonly, obstruction, as seen in obliterative bronchiolitis, is the hallmark of diffuse lung disease of RA. In this situation, forced expiratory volume in one second (FEV1) is reduced out of proportion to FVC, with an FEV1/FVC ratio < 0.8 , and there may be hyperinflation and gas trapping. As a diagnostic tool, a PFT is insufficient and all RA patients with concern for ILD should undergo HRCT.

The superiority of HRCT over chest radiographs, PFTs, and bronchoalveolar lavage (BAL) in identifying ILD has been consistently demonstrated in research studies, although limited data exist regarding its exact sensitivity in detecting RA-associated ILD (e.g. Biederer et al., 2004). Nevertheless, HRCT is the most sensitive non-invasive modality for the diagnosis of ILD in patients with RA.

The HRCT findings of UIP pattern, particularly in patients with a high pre-test probability based on clinical history, physical exam findings and an abnormal PFT, confirms the diagnosis of RA-ILD with great confidence (Martinez 2006). This is in part owing to the unique radiological features of UIP and it likely being the most common RA-associated ILD pattern (Lee et al., 2005). HRCT features of UIP in an RA patient are highly indicative of histologic findings of UIP on surgical lung biopsy, but could also be associated with fibrotic NSIP. Regardless, the presence of UIP findings unequivocally establishes the diagnosis of an ILD. The HRCT findings of NSIP pattern also has high diagnostic value albeit to a lesser extent, due to its less specific radiological features (MacDonald et al., 2001). Radiological uncertainty, inconsistency between diagnostic modalities or with clinical presentation, necessitates additional investigations including consideration of a surgical lung biopsy.

Surgical biopsy of lung parenchyma is now commonly performed by video-assisted thoracoscopic surgery (VATS). Although surgical risks should always be assessed for the individual patient, surgical lung biopsy, particularly VATS biopsy, is a relatively safe procedure that is well tolerated (Zhang & Liu, 2010). In light of its safety profile and high diagnostic yield, surgical lung biopsy should be strongly considered in the face of clinically important diagnostic uncertainty (See Figure 4 for summary of screening and diagnosis).

Bronchoalveolar lavage (BAL), a method to sample the lungs' terminal airways, transbronchial lung biopsy, and radiology-guided needle biopsy, usually provide samples that are generally insufficient to adequately characterize or classify ILD (Biederer et al., 2004). The main role of BAL in immunosuppressed patients with parenchymal

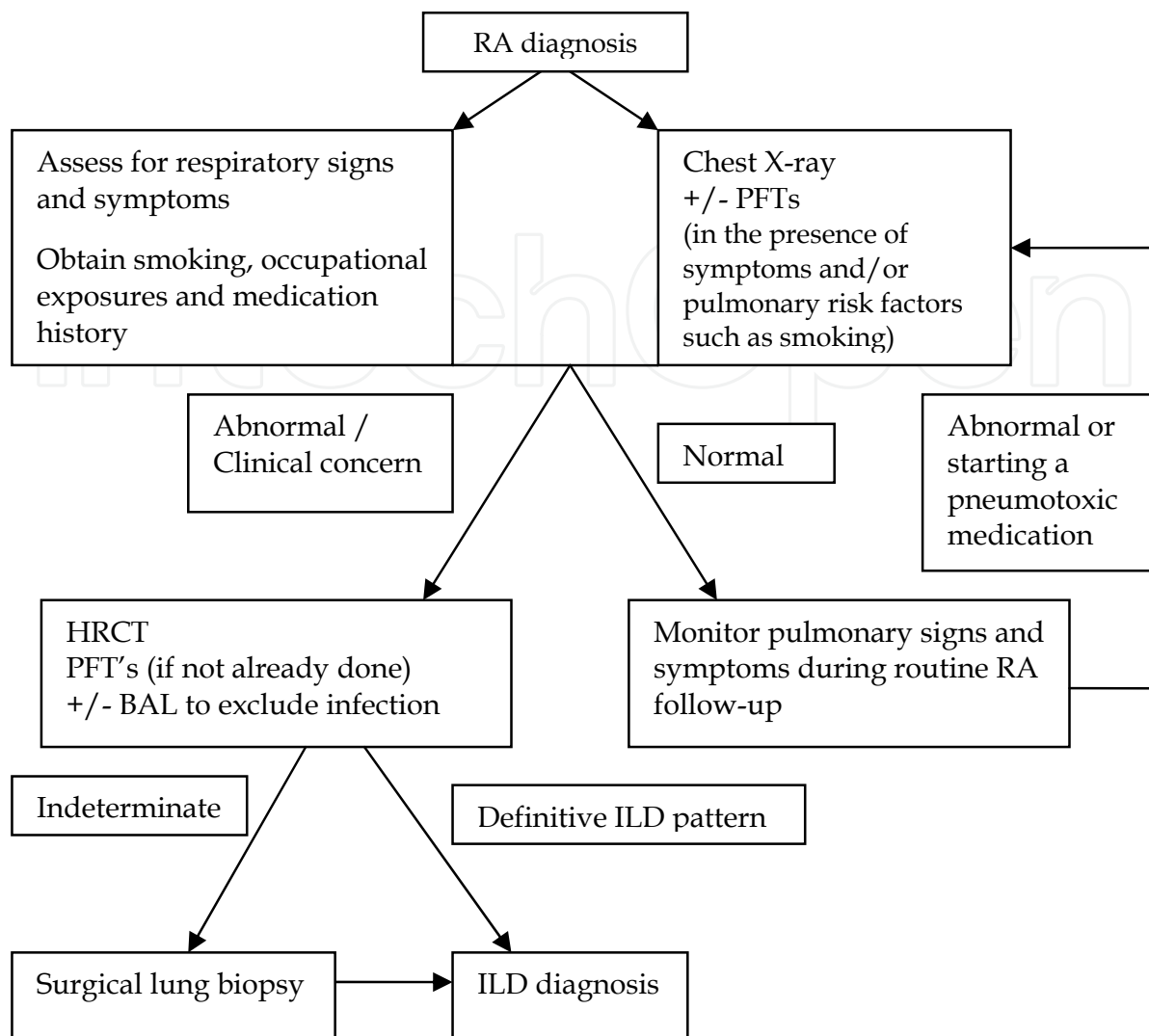


Fig. 4. Proposed screening protocol for RA-ILD and diagnosis flowchart

abnormalities on HRCT is to rule out infection and assess for malignancy. Therefore, unless infection is suspected, surgical lung biopsy is the preferred method of histologic detailed characterization of RA-associated ILD.

2.6 Management

A three-pronged approach should be considered for management of RA patients with ILD. The first phase of this approach is education and consideration of transplantation evaluation. RA patients diagnosed with ILD need to be counseled about the potentially progressive nature of this condition as well as its associated morbidity and mortality. In the setting of idiopathic pulmonary fibrosis (IPF), referral for lung transplantation evaluation should generally be considered relatively early in the disease course provided that there are no obvious contraindications for transplant. Predictors of poor prognosis and the need for more rapid assessment for lung transplant include a diffusing capacity less than 39%, documented deterioration in FVC by at least 10% or diffusing capacity by at least 15% over 6 months, new onset exertional oxygen desaturation below 88%, progression of symptoms, or advanced disease with evidence of significant honeycombing on HRCT at first presentation

(Orens et al., 2006). Although limited data is available for RA associated UIP, an analogous approach should be considered since UIP in RA patients seems to carry the same poor prognosis as IPF, worse than any other ILD (Park et al., 2007). RA patients with UIP are also more likely to experience acute exacerbations (Dawson et al., 2002, Park et al., 2007b), analogous to the recently defined acute exacerbations of IPF (Collard et al., 2007), and they seem to be less responsive to pharmacological treatments (Nannini et al., 2008). Patients with NSIP tend to have a better prognosis, and so transplant evaluation is usually reserved for patients with significant progression or more advanced disease that has not responded to therapy.

The second part of management is supportive care. Clinicians should ensure that patients receive annual influenza, as well as regular pneumococcal vaccinations. Smoking cessation and avoidance of passive smoke exposure are paramount as they exert a deleterious effect on disease progression. Assessment of the need for home oxygen should be done in the face of worsening respiratory status. For patients with impaired respiratory function, who plan to travel by air, clinicians should consider assessing their need for supplemental oxygen at altitude even in those who do not meet criteria for oxygen at sea level. Applications for disability, handicapped parking, and referrals to patient support groups should be implemented early in the management phase.

Finally, an immunosuppressive treatment regimen should be implemented. Currently, clinicians do not have the benefit of evidence-based guidelines to direct the pharmacological management of RA-associated ILD and current treatments rely to a great extent on clinical experience and evidence from management of ILD in other connective tissue diseases, such as scleroderma. In general, the use of glucocorticoids constitutes the basis of pharmacological management. However, their efficacy as monotherapy is limited and patients would typically require the addition of another immune modulating pharmacological agent. Oral prednisone is typically the first component of treatment with a starting dose ranging between 0.5 to 1 milligrams per kilogram of body weight daily. Patients should then be monitored closely for clinical changes as well as for possible adverse effects related to the use of high-dose glucocorticoids. It is prudent to obtain a baseline bone mineral density (BMD) and screen patients for the development of diabetes once treatment commences. Bone protection therapy with calcium and Vitamin D supplements should be given to all patients. Patients with an abnormal BMD at baseline should also be given a bisphosphonate. Prophylaxis against pneumocystis pneumonia (PCP) should be employed with long term prednisone use of at least 30 mg/day, in particular, if there is concomitant use of a cytotoxic agent (Yale & Limper, 1996).

Serial PFTs and chest HRCT scans are used to objectively assess clinical response to treatment. In the absence of clear guidelines as to the frequency of these tests, clinical judgment should be exercised. In general, a reasonable approach would be to have the initial follow-up at 8 to 12 weeks with repeat PFTs and subsequent follow-up every 3 to 6 months thereafter. Chest imaging might be initially repeated as early as 6 months after initiating immunosuppressive therapy, but typically follow-up imaging is performed annually with low-radiation dose CT scans. Repeat imaging should also be considered at any time when clinically important or unexplained changes occur in the patient's clinical course. Time to clinical response is variable and while some patients may experience improvement within a span of a few weeks, most will require several months, while still others may have very limited benefit.

A steroid-sparing immunosuppressive agent, should be considered relatively early in cases of RA-ILD. Clinical worsening on glucocorticoid monotherapy or significant burden of parenchymal involvement, as typically evidenced by >20% involvement on HRCT chest or <70% FVC, warrants the addition of a second immunosuppressive agent (Goh et al., 2008). Recommendations with respect to the second immunosuppressive agent are derived from studies of scleroderma-associated ILD (SSc-ILD). Oral cyclophosphamide, at doses between 1-2mg/kg body weight daily, is used for extensive disease although its efficacy may be modest at best and its use associated with significant adverse effects. Monthly intravenous pulses of cyclophosphamide may be a reasonable alternative to oral cyclophosphamide as it has a similar efficacy profile, but lower toxicity when compared to oral therapy (Hoyles et al., 2006). Azathioprine can also be used, but may be reserved for patients with less severe disease or in those who are intolerant of cyclophosphamide, with an initial dose ranging between 2 - 3 milligrams per kilogram daily.

Various other immune-modulating therapies have been tried for the treatment of RA-ILD, none of which is sufficiently supported by empirical data to warrant routine use in practice. Application of these therapies to RA-ILD typically stems from clinical experience applying these treatments in other CTD-ILD.

One such example is mycophenolate, which has recently been described in case series to be associated with stabilization and potential improvement in lung function in patients with CTD-ILD (Saketkoo & Espinoza, 2008; Swigris et al., 2006) and SSc-ILD (Zamora et al., 2008). However, one limitation with the use of mycophenolate in the setting of RA is that while it might provide lung function benefit, it does not treat joint inflammation, and, therefore, often necessitates the use of higher corticosteroid use to manage RA disease activity. Thus, we recommend that mycophenolate should be used as a second-line agent in the management of RA-ILD. In contrast, methotrexate, a common agent used in many CTD, has been shown to not only provide no clinical benefit in RA-ILD, but may be potentially harmful by leading to ILD disease progression (Gochuico et al., 2008). Therefore, methotrexate should not be used in the setting of RA-ILD. The anti-CD20 antibody, Rituximab, has also been suggested based on its use in other CTD- and vasculitis- associated lung involvement (Brulhart et al., 2006, Stasi et al., 2006). However, caution is advised in light of concerns raised over the risk of pneumonitis with rituximab (Leon et al., 2004), including specifically in RA-ILD patients (Jadon et al., 2008). Anti-TNF alpha antibodies, tyrosine-kinase inhibitors (Distler et al., 2008) and anti-IL6 receptor antibody are also being considered for RA-associated ILD, but data is very limited and their safety in this setting has not been confidently established. The use of other agents, such as cyclosporine and hydroxychloroquine, has also been suggested yet with very limited empirical evidence (Chang et al., 2002).

Patients presenting with severe clinical symptoms, particularly with evidence of AIP, may receive an initial course of intravenous methylprednisolone pulses at 7 to 10 milligrams per kilogram of body weight. Intravenous cyclophosphamide at 10 to 15 milligrams per kilogram can be initiated concomitantly in this setting if no other contraindications exist (Kelly & Saravanan 2008). Once clinically stable, patients should then be switched to oral therapy.

Several adjuvant therapies have been suggested for RA-ILD, extrapolated from practices used to treat idiopathic or other CTD subtypes with ILD. One such treatment is N-acetylcysteine (NAC), which is commonly used in patients with idiopathic pulmonary fibrosis (IPF). It is believed to exert an anti-oxidant effect as well as have mucolytic

properties. While limited evidence supports its efficacy in patients with IPF (Demedts et al., 2005), there is currently no evidence-based rationale for its use in RA-ILD. The use of anticoagulation in patients with RA-ILD has also been suggested in light of the increased risk of thrombosis associated with IPF (Hubbard et al., 2008). In the absence of empirical evidence, the decision to use anticoagulation should be made based on clinical risk assessment of each patient's individual risk factors and should not be initiated without direct guidance from a transplant centre in a patient being considered for lung transplantation.

3. Pulmonary inflammation and the pathogenesis of RA

RA has traditionally been conceptualized as an autoimmune disease of the synovium associated with an inappropriate excessive inflammatory response leading to systemic complications. Although the exact etiology of RA remains to be elucidated, it is now evident that RA's underlying pathophysiology is far more complex and extends beyond the traditional view that the disease begins in the synovium. Growing evidence suggest that the systemic inflammatory response and antibody formation precede synovial involvement and clinical symptoms of RA (van de Sande et al., 2011). In fact, antibodies associated with RA, including IgM rheumatoid factor and anti-citrullinated protein antibodies (ACPA) (a.k.a. anti-cyclic citrullinated protein, anti-CCP, antibodies) appear to be present in the serum of RA patients many years before the onset of clinical disease (Nielen et al., 2004, Rantapää-Dahlqvist et al., 2003).

The key to understanding the immunological processes believed to underlie the development of RA is the concept of citrullination. This refers to the post-translational modification of proteins whereby the amino acid arginine is de-aminated and converted to citrulline by the enzyme peptidylarginine deiminase (PAD) (Yamada et al., 2005). This conversion occurs intracellularly to affect the electrical charge of the protein, thereby altering its folding. In order to develop antibodies to citrullinated peptides, the immune system must be exposed to these altered proteins, which occurs following cell death, often incited by insult to the cell wall such as in the context of inflammation. The identity of citrullinated autoantigens is increasingly known, with the leading candidates for the development of RA being alpha-enolase, filaggrin, and vimentin (Schellekens et al., 2000, van Venrooij WJ et al., 2008). Although it has been hypothesized that the primary tissue site of citrullination for development of RA is the joint (synovium), it is becoming increasingly recognized that other tissue sites may be involved in the pathogenesis of RA including the lung and oral mucosa (Bingham et al., 2010, Bongartz et al., 2007). In this section, we will highlight the mechanisms of how development of autoimmunity and RA is not restricted to processes in the joint and how pulmonary inflammation may incite the development of RA.

3.1 Genetic risk of pulmonary disease and of RA

Genetics is known to play an important role in the development of RA and its contribution is estimated to be around 30% and, in some studies, up to 60% (MacGregor et al., 2000). The strongest genetic association with RA has been mapped to a gene area on chromosome 6 known as the Human Leukocyte Antigen (HLA) locus (a.k.a. Major Histocompatibility Complex, MHC) (Zanelli et al., 2000). These genes encode various proteins that play important immunological roles, including in the key distinction of self from foreign. Among the HLA loci, the HLA-DRB1 alleles have been shown to have strong association with RA

(Zanelli et al., 2000), although emerging data now also point to other loci, particularly HLA-DPB1, as independently conferring increased risk for ACPA-positive RA (Ding et al., 2009). Common to the multiple HLA-DRB1 alleles found to be associated with RA, is a shared amino-acid sequence, or motif, which was thus named the 'shared epitope' (SE) (Gregersen et al., 1987). The presence of SE alleles is known to be strongly associated with susceptibility to RA (du Montcel et al., 2005) and the presence of ACPA (Van der Helm-van Mil et al., 2006). The association between SE alleles and RA has been found to be significantly influenced by smoking, particularly, though not exclusively, in the presence of ACPA (Padyukov et al., 2004). Recent evidence suggests that the association between smoking and increased risk of ACPA-positive RA with SE alleles is dose-dependent, where individuals with over 20 pack-year smoking history have a 40 times increased risk of ACPA-positive RA if they carry the double SE alleles compared to non-smokers without the SE alleles (Källberg et al., 2011).

Finally, of note, existing evidence also suggest that certain other HLA-DR alleles, particularly HLA-DR4, are associated with the development of lung disease in RA patients, independent of smoking (Scott et al., 1987).

3.2 Importance of auto-antibodies to citrullinated peptides

In addition to being an apparent predictive marker for the development of RA, the presence of ACPA in patients also appear to be associated with a greater risk of developing extra-articular manifestations, including specifically lung serositis and pulmonary fibrosis (Alexiou et al., 2008, Turesson et al., 2007). Moreover, a recent study by Bongartz et al., (2007) included immunohistochemical examination of lung biopsies from 18 patients with RA-ILD and revealed the presence of citrullinated proteins in 8 (44%) of these patients (Bongartz et al., 2007). The exact identity of the citrullinated autoantigen was not identified; moreover, citrullination did not show any significant association with factors such as smoking, disease severity, histological subtype, degree of inflammation, or steroid use (Bongartz et al., 2007). The findings of citrullinated proteins in lung samples from non-RA patients with idiopathic ILD in the same study suggest that this process is not unique to RA and likely reflects a non-specific response to tissue injury and inflammation. The key difference, therefore, lies in the fact that, in RA patients, an aberrant immune response occurs by which ACPA are generated in response to these proteins, which in turn result in pathology. The challenge is then to identify the potential factors that might mediate this aberrant process.

3.3 Environmental triggers of pulmonary inflammation

Smoking has been firmly established as a causative agent in lung inflammation and injury. It has also been shown to be associated with both the development of RA, accounting for nearly 20% of the risk, and worse disease course of RA, even years after smoking cessation (Albano et al., 2001, Harrison, 2002). These two seemingly unrelated adverse effects of smoking on lung and RA are in fact intricately connected beyond the mere aggravated inflammatory response triggered by smoking. Smoking has been shown to be associated with an increase in pulmonary protein citrullination, which appears to be mediated by increase in PAD enzyme expression, particularly PAD2, in both parenchymal and bronchial tissue (Makrygiannakis et al., 2008). Moreover, as outlined previously (see section 3.1 Genetic risk of pulmonary disease and of RA) a strong, dose-dependent, association has been established between smoking and the presence of ACPA in RA patients (Källberg, et

al., 2011). These findings point to a possible pathogenesis of pulmonary inflammation in RA patients in which ACPA react with the increased presence of citrullinated proteins in pulmonary tissue that were the result of pulmonary injury caused by environmental trigger such as smoking. Similar pathogenic processes were found with other environmental exposures such as silica (Stolt et al., 2010).

However, current evidence suggests that the interplay between synovium and lung is in fact far more complex. The findings of ACPA in ILD patients without clinical evidence of articular symptoms suggest that these antibodies can be generated independent of synovial involvement. This was further corroborated by a prospective study of ACPA-positive patients, who were found to have no radiological or histological evidence of synovial inflammation (van de Sande et al., 2011). In this study, 13 patients with positive RA serology (IgM rheumatoid factor and/or ACPA) but without clinical evidence of arthritis underwent knee MRI and arthroscopic synovial tissue biopsy with immuno-histochemistry testing. No significant differences were found when the results were compared to those obtained from a group of individuals with negative RA serology. After a median follow-up period of 3 months (range 1-6 months), 4 of these patients developed clinical evidence of arthritis. This demonstrated that the synovium in ACPA-positive patients is initially normal, even in patients who later develop clinical arthritis. In addition, existing evidence suggests that a proportion of patients with positive RA serology may already have HRCT parenchymal lung changes at time of RA diagnosis (Gabbay et al., 1997, Metafratzi et al., 2007, Reynsdottir et al., 2011). In fact, a retrospective study by Gizinski et al. (2009) showed that positive RA serology can be found in smokers with ILD without symptoms and signs of RA, but who may later develop RA. Therefore, clinicians assessing patients with positive RA serology but no articular symptoms should nevertheless inquire and be mindful of respiratory symptoms in these patients.

Taken together, these findings evoke a conceptual paradigm different from the long-held view of pulmonary inflammation being an extra-articular manifestation of synovial inflammation. In this paradigm, synovial inflammation is seen as a down-stream consequence of an aberrant immunological pulmonary process triggered by insults, such as smoking, that lead to the formation of ACPA. The ACPA, in turn, react to citrullinated proteins formed in the synovium due to a different, independent, insult such as mechanical or infectious joint injury (See figure 5). Further research is needed and is underway to elucidate this intricate interplay between the lung and the synovium as well as the possibility that such an interaction with the synovium may not only be limited to the lung.

3.4 Pre-RA and its clinical implications

The concept of 'early RA' has long been clinically utilized to denote patients in the early stages of the disease. However, the synovium of patients with 'early RA' already displays radiological (van der Heijde, 1995) and histological (Tak, 2001) evidence of chronic inflammation. Therefore, the concept of 'pre-RA' has been suggested to describe the time period before the onset of clinical signs and symptoms of synovial inflammation (van de Sande et al., 2011). During this time, patients may already have evidence of sub-clinical systemic inflammation, such as elevated non-specific inflammatory markers (e.g. C-reactive protein), and may be tested positive for the presence of ACPA. As previously described, the presence of ACPA can occur in the absence of synovial inflammation and may, in fact, precede clinical manifestation of arthritis by longer than a decade (Nielen et al., 2004). It is presumably during this time interval that the second, independent, injury occurs, which

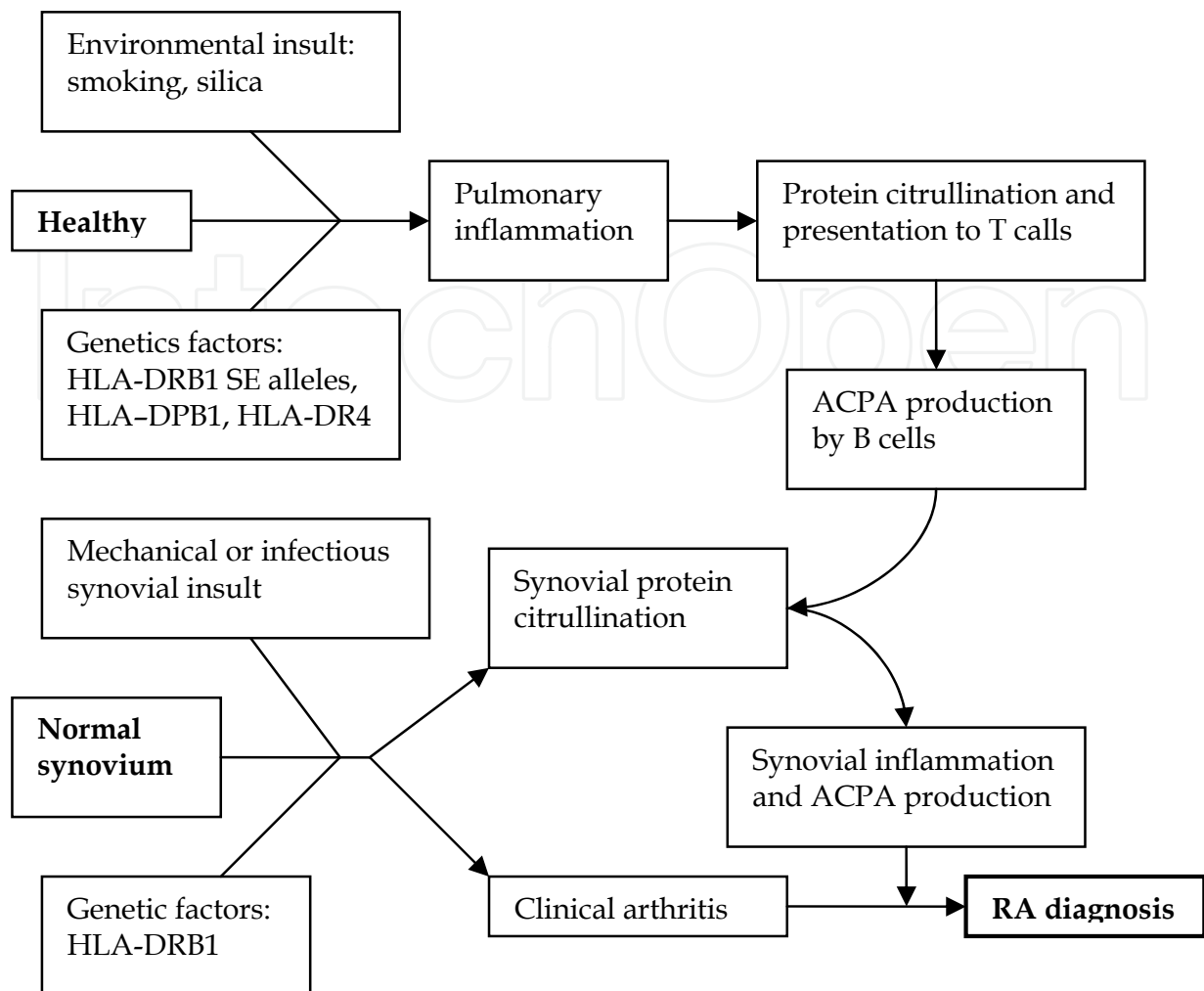


Fig. 5. The postulated interaction between genetics, environmental factors, pulmonary inflammation and protein citrullination in the pathogenesis of RA

leads to synovial protein citrullination and the resulting epitope spreading and development of synovial inflammation.

This multi-factorial model of RA development raises the potential for prevention, which may be aimed at averting, slowing, or potentially reversing the progression towards clinical RA. The first and foremost preventative measure based on the available evidence is avoidance of tobacco smoking. Since environmental exposures, such as smoking and silica inhalation, appear to play a key role in the initial formation of ACPA, avoidance of these triggers may potentially abort the development of RA in genetically susceptible individuals. Further research is necessary to better understand the initial development of ACPA and explore the potential for prevention, particularly in genetically susceptible individuals. The existence of a 'pre-RA' stage also provides an opportunity for potential pharmacological interventions that might prevent or delay the development of synovial inflammation. The identification of the second event that results in synovial protein citrullination should also be a focus of future research and preventative efforts.

The emerging evidence of the close interplay between the lungs and the synovium together with the growing recognition of the clinical significance of pulmonary complications in RA patients, including RA-ILD, suggest that RA patients may benefit from a multidisciplinary

approach to their management. Although such collaboration appears to be most beneficial to RA patients with pulmonary complications, it may expand in the future to include patients with pulmonary inflammation at risk of RA by virtue of their genetics or ACPA presence, without yet having any articular manifestations.

4. Summary

Our understanding of RA and RA-ILD is quickly evolving in light of ongoing research. RA-ILD is increasingly recognized as a prevalent clinical entity with significant associated morbidity and mortality, which poses both diagnostic and therapeutic challenges to clinicians and calls for increased attention to pulmonary abnormalities in RA patients. In addition, as highlighted in this chapter, growing evidence also suggests that pulmonary inflammation plays an important role in the etiology of RA, particularly in autoantibody-positive patients, with evidence of lung injury preceding synovial inflammation. The complex interplay between the lung and the synovium remains to be further elucidated but it is clear that synovial inflammation can no longer be viewed as an isolated, independent process. The likely multi-factorial nature of this interplay not only raises the potential for new therapeutic targets in RA, but also raises the prospect for prevention. Furthermore, it also raises the question of whether similar complex interactions exist between the synovium and other organs. Future research is currently underway and would hopefully provide answers to these important questions, leading to a better understanding and management of RA.

5. Key points

1. RA is a common systemic inflammatory disorder affecting 1% of the general population
2. RA-ILD is a serious extra-articular manifestation that confers significant morbidity and mortality
3. Clinicians need to be vigilant to screen for respiratory signs and symptoms in RA patients as these may represent an underlying ILD
4. The diagnosis of RA-ILD can be made with HRCT but, in some cases, diagnostic uncertainty necessitates a surgical lung biopsy
5. UIP and NSIP are the most common histopathological patterns of RA-ILD
6. The treatment of RA-ILD is three-pronged, including education and transplant evaluation, supportive care and the use of immunosuppressive medications
7. Pulmonary inflammation, protein citrullination and the formation of auto-antibodies to citrullinated peptides may play a key role in the pathogenesis of RA
8. The interaction of genetics and environmental factors is fundamental to this process
9. Growing evidence point to a complex, multi-factorial interaction between the lung and the synovium, with lung injury preceding synovial inflammation
10. Further research is necessary to delineate this complex interplay and explore its clinical implications

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7. References

- Albano SA, Santana-Sahagun E, & Weisman MH. (2001). Cigarette smoking and rheumatoid arthritis. *Semin Arthritis Rheum*, Vol.31, pp. 146-159.
- Alexiou I, Germeis A, Koutroumpas A, Kontogianni A, Theodoridou K, & Sakkas L. (2008). Anti-cyclic citrullinated peptide-2 (CCP2) autoantibodies and extra-articular manifestations in Greek patients with rheumatoid arthritis. *Clin Rheumatol*, Vol. 27, pp. 511-513
- Biederer J, A. Schnabel, C. Muhle, W. L. Gross, M. Heller, & M. Reuter. (2004). Correlation between HRCT findings, pulmonary function tests and bronchoalveolar lavage cytology in interstitial lung disease associated with rheumatoid arthritis. *Eur Radiol*, Vol. 14, pp.272-280
- Bingham C, Reynolds M, Giles J, Felipe B, Fox-Talbot J, Halushka K, & Marc K. (2010). Citrullination and Peptidylarginine Deiminase (PAD) Expression Is Detected in the Oral Mucosa and Periodontium in the Absence of Rheumatoid Arthritis. *Arthritis Rheum*, Vol. 62 Suppl 10, pp. 1074
- Bongartz T, Cantaert R, Atkins P, Harle J, Myers C, Turesson J, Ryu D, & Matteson E. (2007). Citrullination in extra-articular manifestations of rheumatoid arthritis. *Rheumatology*, Vol. 46, pp. 70-75
- Bongartz T, Nannini C, Medina-Velasquez Y, Achenbach S, Crowson C, Ryu J, Vassallo R, Gabriel S, & Matteson E. (2010). Incidence and Mortality of Interstitial Lung Disease in Rheumatoid Arthritis-A Population-Based Study. *Arthritis & Rheumatism*, Vol. 62, pp 1583-1591.
- Bouros D, Nicholson A, Polychronopoulos V, du Bois R. Acute interstitial pneumonia (2000). *Eur Respir J* Vol. 15, pp. 412-418.
- Brown K. (2007). Rheumatoid lung disease. *Proc Am Thorac Soc*, Vol. 4, pp.443-448.
- Brulhart L, Waldburger JM, & Gabay C. (2006). Rituximab in the treatment of anti-synthetase syndrome. *Ann Rheum Dis*, Vol. 65, pp. 974 -5
- Chang HK, Park W, & Ryu DS. (2002). Successful treatment of progressive rheumatoid interstitial lung disease with cyclosporine: a case report. *J Korean Med Sci*, Vol.17, pp. 270-273
- Collard H, Moore B, Flaherty K, Brown K, Kaner R, King T, Lasky J, Loyd J, Noth I, Olman M, Raghu G, Roman J, Ryu J, Zisman D, Hunninghake G, Colby T, Egan J, Hansell D, Johkoh T, Kaminski N, Kim D, Kondoh Y, Lynch D, Müller-Quernheim J, Myers J, Nicholson A, Selman M, Toews G, Wells A, & Martinez F. (2007). Acute Exacerbations of Idiopathic Pulmonary Fibrosis. *Am. J. Respir. Crit. Care Med*, Vol. 176, pp. 636-643
- Cottin V, Nunes H, Mouthon L, Gamondes D, Lazor R, Hachulla E, Revel D, Valeyre D, & Cordier JF (2011). Combined Pulmonary Fibrosis and Emphysema Syndrome in Connective Tissue Disease. *Arthritis & Rheumatism*, Vol.63, pp. 295-304.
- Cushley MJ, Davison AG, DuBois RM, Flower C, Greening A, Ibrahim N, Johnston I, Mitchell D, & Pickering A.(1999). The diagnosis, assessment and treatment of diffuse parenchymal lung disease in adults: British Thoracic Society recommendations. *Thorax*, Vol.54(suppl 1), pp.S1-14.
- Dawson J, Fewins H, Desmond J, Lynch M, & Graham D. (2002). Predictors of progression of HRCT diagnosed fibrosing alveolitis in patients with rheumatoid arthritis. *Ann Rheum Dis*, Vol. 61, pp. 517-521

- Demedts M, Behr J, Buhl R, Costabel U, Dekhuijzen R, Jansen H, MacNee W, Thomeer M, Wallaert B, Laurent F, Nicholson A, Verbeken E, Verschakelen J, Flower C, Capron F, Petruzzelli S, De Vuyst P, van den Bosch J, Rodriguez-Becerra E, Corvasce G, Lankhorst I, Sardina M, & Montanari M. (2005). High-dose acetylcysteine in idiopathic pulmonary fibrosis. *N Engl J Med*, Vol. 353, pp. 2229 -2242
- Ding B, Padyukov L, Lundström E, Seielstad M, Plenge R, Oksenberg J, Gregersen P, Alfredsson L, & Klareskog L. (2009). Different Patterns of Associations With Anti-Citrullinated Protein Antibody-Positive and Anti-Citrullinated Protein Antibody-Negative Rheumatoid Arthritis in the Extended Major Histocompatibility Complex Region. *Arthritis Rheum*, Vol. 60, pp. 30-38.
- Distler J, Manger B, Spriewald B, Schett G, & Distler O. (2008). Treatment of pulmonary fibrosis for 20 weeks with imatinib mesylate in a patient with mixed connective tissue disease. *Arthritis Rheum*, Vol. 58, pp. 2538-2542
- Dixon W, Hyrich K, Watson K, Lunt M, BSRBR Control Centre Consortium, & Symmons D. (2010). Influence of anti-TNF therapy on mortality in patients with rheumatoid arthritis-associated interstitial lung disease: results from the British Society for Rheumatology Biologics Register. *Ann Rheum Dis*, Vol.69, pp. 1086-1091
- du Montcel S, Michou L, Petit-Teixeira E, Osorio J, Lemaire I, Lasbleiz S, Pierlot C, Quillet P, Bardin T, Prum B, Cornelis F, & Clerget-Darpoux F. (2005). New Classification of HLA-DRB1 Alleles Supports the Shared Epitope Hypothesis of Rheumatoid Arthritis Susceptibility. *Arthritis&Rheumatism*, Vol. 52, pp. 1063-1068
- Gabbay E, Tarala R, Will R, Carroll G, Adler B, Cameron D, & Lake F. (1997). Interstitial Lung Disease in Recent Onset Rheumatoid Arthritis. *Am J Respir Crit Care Med*, Vol. 156, pp. 528-535.
- Gabriel SE. (2001). The epidemiology of rheumatoid arthritis. *Rheum Dis Clin North Am*, Vol. 27, pp. 269-281
- Gizinski AM, Mascolo M, Loucks JL, Kervitsky A, Meehan RT, Brown KK, Holers V, & Deane KD. (2009). Rheumatoid arthritis (RA)-specific autoantibodies in patients with interstitial lung disease and absence of clinically apparent articular RA. *Clin Rheumatol*, Vol. 28, pp. 611-613.
- Gochuico BR, Avila NA, Chow CK, Novero LJ, Wu HP, Ren P, MacDonald SD, Travis WD, Stylianou MP, & Rosas IO.(2008). Progressive preclinical interstitial lung disease in rheumatoid arthritis. *Arch Intern Med*, Vol. 168, pp. 159-166
- Goh N, Desai S, Veeraraghavan S, Hansell D, Copley S, Maher T, Corte T, Sander C, Ratoff J, Devaraj A, Bozovic G, Denton C, Black C, du Bois R, & Well A. (2008). Interstitial Lung Disease in Systemic Sclerosis: a Simple Staging System. *Am J Respir Crit Care Med*, Vol. 177, pp. 1248 - 1254.
- Gregersen PK, Silver J, & Winchester RJ. (1987). The shared epitope hypothesis: an approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis [current comment]. *Arthritis Rheum*, Vol. 30, pp.1205-1213.
- Hakala, M. (1988) Poor Prognosis in Patients with Rheumatoid Arthritis Hospitalized for Interstitial Lung Fibrosis. *Chest*, Vol. 93, pp. 114-118.
- Hansen JE, Sue DY, & Wasserman K (1984). Predicted values for clinical exercise testing. *Am Rev Respir Dis*, Vol. 129(Suppl), pp. S49-S55.
- Harrison BJ. (2002). Influence of cigarette smoking on disease outcome in rheumatoid arthritis. *Curr Opin Rheumatol*, Vol. 14, pp. 246-252.

- Hartman T, Swensen S, Hansell D, Colby T, Myers J, Tazelaar H, Nicholson A, Wells A, Ryu J, Midthun D, du Bois R, & Müller N (2000). Nonspecific interstitial pneumonia: variable appearance at high-resolution chest CT. *Radiology* Vol. 217, pp. 701-705
- Hilliquin P, Renoux M, Perrot S, Puéchal X, & Menkès CJ (1996). Occurrence of pulmonary complications during methotrexate therapy in rheumatoid arthritis. *Br J Rheumatol.* Vol. 35, pp. 441-445.
- Hoyles RK, Ellis RW, Wellsbury J, Lees B, Newlands P, Goh NS, Roberts C, Desai S, Herrick AL, McHugh NJ, Foley NM, Pearson SB, Emery P, Veale DJ, Denton CP, Wells AU, Black CM, & du Bois RM. (2006). A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. *Arthritis Rheum.* Vol. 54, pp. 3962-3970.
- Hubbard R, Smith C, Le-Jeune I, Gribbin J, & Fogarty A. (2008). The Association between Idiopathic Pulmonary Fibrosis and Vascular Disease A Population-based Study. *Am J Respir Crit Care Med*, Vol. 178, pp. 1257-1261
- Imokawa S, Colby T, Leslie K, & Helmers R. (2000). Methotrexate pneumonitis: review of the literature and histopathological findings in nine patients. *Eur Respir J*, Vol. 15, pp. 373-381
- Jadon D, Chan A, & McNally J. (2008). Life threatening leflunomide pneumonitis in a patient on rituximab. *Rheumatology*, Vol. 47(2), ii158 (no. 549)
- Källberg H, Ding B, Padyukov L, Bengtsson C, Rönnelid J, Klareskog L, & Alfredsson L. (2011). Smoking is a major preventable risk factor for rheumatoid arthritis: estimations of risks after various exposures to cigarette smoke. *Ann Rheum Dis*, Vol. 70, pp. 508-511
- Katzenstein AL, Myers JL, & Mazur MT. Acute interstitial pneumonia. A clinicopathologic, ultrastructural, and cell kinetic study. (1986) *Am J Surg Pathol* Vol. 10, pp. 256-267.
- Katzenstein AL & Myers JL. (1998). Idiopathic pulmonary fibrosis: clinical relevance of pathologic classification. *Am J Respir Crit Care Med*, Vol. 157, pp. 1301-1315.
- Kelly C & Saravanan V. (2008). Treatment strategies for a rheumatoid arthritis patient with interstitial lung disease. *Expert Opin. Pharmacother*, Vol. 9, pp. 3221-3230.
- Kremer JM, Alarcón GS, Weinblatt ME, Kaymakcian MV, Macaluso M, Cannon GW, Palmer WR, Sundry JS, St Clair EW, Alexander RW, Smith GJ, & Axiotis CA. (1997). Clinical, laboratory, radiographic, and histopathologic features of methotrexate-associated lung injury in patients with rheumatoid arthritis: a multicenter study with literature review. *Arthritis Rheum.* Vol. 40, pp. 1829-1837.
- Lee HK, Kim DS, Yoo B, Seo J, Rho J, Colby T, & Kitaichi M. (2005). Histopathologic pattern and clinical features of rheumatoid arthritis-associated interstitial lung disease. *Chest*, Vol. 127, pp. 2019-2027
- Leon RJ, Gonsalvo A, Salas R, & Hidalgo NC. (2004). Rituximab-induced acute pulmonary fibrosis. *Mayo Clin Proc*, Vol. 79, pp. 945-56
- MacDonald SLS, Rubens MB, Hansell DM, Copley SJ, Desai SR, du Bois RM, Nicholson AG, Colby TV, & Wells AU. (2001) Nonspecific interstitial pneumonia and usual interstitial pneumonia: comparative appearances at and diagnostic accuracy of thin-section CT. *Radiology* Vol. 221, pp. 600-605.

- MacGregor AJ, Snieder H, Rigby AS, Koskenvuo M, Kaprio J, Aho K, & Silman AJ. (2000). Characterizing the quantitative genetic contribution to rheumatoid arthritis using data from twins. *Arthritis Rheum*, Vol. 43, pp. 30-37.
- Makrygiannakis D, Hermansson M, Ulfgren AK, Nicholas AP, Zendman AJ, Eklund A, Grunewald J, Skold CM, Klareskog L, & Catrina AI. (2008). Smoking increases peptidylarginine deiminase 2 enzyme expression in human lungs and increases citrullination in BAL cells. *Ann Rheum Dis*, Vol. 67, pp.1488-1492.
- Manjunatha Y, Seith A, Kandpal H, & Das C. (2010). Rheumatoid Arthritis: Spectrum of Computed Tomographic Findings in Pulmonary Diseases. *Curr Probl Diagn Radiol*, Vol. 39, pp. 235-246.
- Maradit-Kremers H, Nicola PJ, Crowson CS, Ballman KV, & Gabriel SE. (2005) Cardiovascular death in rheumatoid arthritis: a population-based study. *Arthritis Rheum*, Vol. 52, pp. 722-732.
- Martinez F. (2006). Idiopathic Interstitial Pneumonias Usual Interstitial Pneumonia versus Nonspecific Interstitial Pneumonia. *Proc Am Thorac Soc*, Vol. 3, pp 81-95.
- Metafratzi Z, Georgiadis A, Ioannidou C, Alamanos Y, Vassiliou M, Zikou A, Raptis G, Drosos A, & Efremidis S. (2007). Pulmonary involvement in patients with early rheumatoid arthritis. *Scandinavian Journal of Rheumatology*, Vol. 36, pp. 338-344
- Minaur NJ, Jacoby RK, Cosh JA, Taylor G, & Rasker JJ. (2004) Outcome after 40 years with rheumatoid arthritis: a prospective study of function, disease activity, and mortality. *J Rheumatol Suppl*, Vol.69, pp.3-8.
- Nannini C, Ryu JH, & Matteson EL. (2008). Lung disease in rheumatoid arthritis. *Curr Opin Rheumatol*, Vol. 20, pp. 340-346
- Nielen M, van Schaardenburg D, Reesink H, van de Stadt R, van der Horst-Bruinsma I, de Koning M, Habibuw M, Vandenbroucke J, & Dijkmans B.(2004). Specific autoantibodies precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors. *Arthritis Rheum*, Vol. 50, pp. 380 -386.
- Orens J, Estenne M, Arcasoy S, Conte J, Corris P, Egan J, Egan T, Keshavjee S, Knoop S, Kotloff R, Martinez F, Nathan S, Palmer S, Patterson A, Singer L, Snell G, Studer S, Vachieri J, & Glanville A. (2006). International Guidelines for the Selection of Lung Transplant Candidates: 2006 Update – A Consensus Report From the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant*, Vol. 25, pp. 745-755
- Padyukov L, Silva C, Stolt P, Alfredsson L, & Klareskog L. (2004). A Gene-Environment Interaction Between Smoking and Shared Epitope Genes in HLA-DR Provides a High Risk of Seropositive Rheumatoid Arthritis. *Arthritis&Rheumatism*, Vol. 50, pp. 3085-3092
- Pappas D, Giles J, Connors G, Lechtzin N, Bathon J, & Danoff S. (2010). Respiratory symptoms and disease characteristics as predictors of pulmonary function abnormalities in patients with rheumatoid arthritis: an observational cohort study. *Arthritis Research & Therapy*, Vol. 12, pp. R104-114.
- Parambi J, Myers J, & Ryu J. (2006) Diffuse Alveolar Damage: Uncommon Manifestation of Pulmonary Involvement in Patients With Connective Tissue Diseases. *Chest* Vol. 130, pp. 553-558

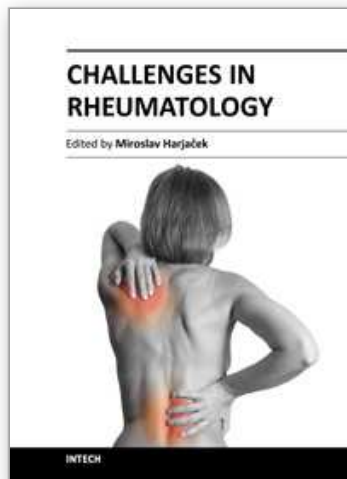
- Park H, Kim S, Park N, Jang S, Kitaichi M, Nicholson A, & Colby T. (2007a). Prognosis of fibrotic interstitial pneumonia: idiopathic versus collagen vascular disease-related subtypes. *Am J Respir Crit Care Med*, Vol. 175, pp.705-711
- Park IN, Kim D, Shim T, Lim C, Lee S, Koh Y, Kim WS, Kim WD, Jang S, & Colby T. (2007b). Acute exacerbation of interstitial pneumonia other than idiopathic pulmonary fibrosis. *Chest*, Vol.132, pp. 214-220
- Parra E, Kairalla R, Ribeiro de Carvalho C, Eher E, & Capelozzi V. (2007) Inflammatory Cell Phenotyping of the Pulmonary Interstitium in Idiopathic Interstitial Pneumonia. *Respiration* Vol. 74 pp.159-169
- Raghu G, Collard H, Egan J, Martinez F, Behr J, Brown K, Colby T, Cordier J, Flaherty K, Lasky J, Lynch D, Ryu J, Swigris J, Wells A, Ancochea J, Bouros D, Carvalho C, Costabel U, Ebina M, Hansell D, Johkoh T, Kim D, King T, Kondoh Y, Myers J, Müller N, Nicholson A, Richeldi L, Selman M, Dudden R, Griss B, Protzko S, & Schunemann H. (2011). An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management. *Am J Respir Crit Care Med*, Vol. 183, pp. 788-824
- Rajasekaran B, Shovlin D, Lord P, & Kelly C. (2001) Interstitial lung disease in patients with rheumatoid arthritis: a comparison with cryptogenic fibrosing alveolitis. *Rheumatology*, Vol.40, pp. 1022-1025.
- Rantapaa-Dahlqvist S, de Jong B, Berglin E, Hallmans G, Wadell G, Stenlund H, Sundin U, & van Venrooij W. (2003). Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. *Arthritis Rheum*, Vol. 48, pp. 2741 - 2749.
- Reynsdottir G, Harju A, Engström M, Nyren S, Sköld M, Eklund A, Grunewald J, Klareskog L, & Catrina A. (2011). Lung changes are present in ACPA positive RA patients already at disease onset. *Ann Rheum Dis*, Vol. 70(Suppl 2), pp. A13
- Saketkoo L & Espinoza L. (2008). Rheumatoid Arthritis Interstitial Lung Disease: Mycophenolate Mofetil as an Antifibrotic and Disease-Modifying Antirheumatic Drug. *Arch Intern Med*, Vol. 168, pp. 1718
- Schellekens GA, Visser H, de Jong BA, van den Hoogen FH, Hazes JM, Breedveld FC, & van Venrooij WJ. (2000). The diagnostic properties of rheumatoid arthritis antibodies recognizing a cyclic citrullinated peptide. *Arthritis Rheum*, Vol.43, pp.155-163
- Scott TE, Wise RA, Hochberg MC, & Wigley FM. (1987). HLA-DR4 and pulmonary dysfunction in rheumatoid arthritis. *Am J Med*, Vol. 82, pp. 765-771
- Segura A, Yuste A, Cercos A, López-Tendero P, Gironés R, Pérez-Fidalgo JA, & Herranz C (2001). Pulmonary fibrosis induced by cyclophosphamide. *Ann Pharmacother*. Vol. 35, pp. 894-897
- Stasi R, Stipa E, Del Poeta G, Amadori S, Newland A, & Provan D. (2006). Long-term observation of patients with anti-neutrophil cytoplasmic antibody-associated vasculitis treated with rituximab. *Rheumatology*, Vol. 45, pp.1432-1436
- St Clair EW, Rice JR, & Snyderman R (1985). Pneumonitis complicating low-dose methotrexate therapy in rheumatoid arthritis. *Arch Intern Med*. Vol. 145, pp. 2035-2038.
- Stolt P, Yahya A, Bengtsson C, Källberg H, Rönnelid J, Lundberg I, Klareskog L, & Alfredsson L. (2010). Silica exposure among male current smokers is associated

- with a high risk of developing ACPA-positive rheumatoid arthritis. *Ann Rheum Dis*, Vol. 69, pp. 1072-1076.
- Suzuki A, Ohosone Y, Obana M, Mita S, Matsuoka Y, Irimajiri S, & Fukuda J. (1994) Cause of death in 81 autopsied patients with rheumatoid arthritis. *J Rheumatol*, Vol. 21, pp. 33-36.
- Swierkot J, & Szechiński J. (2006). Methotrexate in rheumatoid arthritis. *Pharmacol Rep*, Vol. 58, pp. 473-492.
- Swigris JJ, Olson AL, Fischer A, Lynch DA, Cosgrove GP, Frankel SK, Meehan RT, & Brown KK. (2006). Mycophenolate mofetil is safe, well tolerated, and preserves lung function in patients with connective tissue disease-related interstitial lung disease. *Chest*, Vol. 130, pp. 30-36.
- Tak PP. (2001). Is early rheumatoid arthritis the same disease process as late rheumatoid arthritis? *Best Pract Res Clin Rheumatol*, Vol. 15, pp.17 - 26.
- Travis WD, Matsui K, Moss JE, & Ferrans VJ. (2000). Idiopathic nonspecific interstitial pneumonia: prognostic significance of cellular and fibrosing patterns. Survival comparison with usual interstitial pneumonia and desquamative interstitial pneumonia. *Am J Surg Pathol*, Vol. 24, pp. 19-33.
- Tureson C, Jacobsson L, Sturfelt G, Matteson E, Mathsson L, & Rönnelid J. (2007). Rheumatoid factor and antibodies to cyclic citrullinated peptides are associated with severe extra-articular manifestations in rheumatoid arthritis. *Ann Rheum Dis*, Vol. 66, pp.59-64
- van der Heijde DM. (1995). Joint erosions and patients with early rheumatoid arthritis. *Br J Rheumatol*, Vol. 34 (Suppl 2): 74 - 78
- Van der Helm-van Mil AH, Verpoort KN, Breedveld FC, Huizinga TW, Toes RE, & de Vries RR. (2006). The HLA-DRB1 shared epitope alleles are primarily a risk factor for anti-cyclic citrullinated peptide antibodies and are not an independent risk factor for development of rheumatoid arthritis. *Arthritis Rheum*, Vol. 54, pp. 1117-1121.
- van de Sande M, de Hair M, van der Leij C, Klarenbeek P, Bos W, Smith M, Maas M, de Vries N, van Schaardenburg D, Dijkmans B, Gerlag D, & Tak P. (2011). Different stages of rheumatoid arthritis: features of the synovium in the preclinical phase. *Ann Rheum Dis*, Vol. 70, pp. 772-777
- van Venrooij W, van Beers J, & Pruijn G. (2008). Anti-CCP Antibody, a Marker for the Early Detection of Rheumatoid Arthritis. *Ann N Y Acad Sci*, Vol.1143, pp.268-285
- Vourlekis JS, Brown KK, Cool CD, Young DA, Cherniack RM, King TE Jr, & Schwarz MI. (2000). Acute Interstitial Pneumonitis. Case series and review of the literature. *Medicine (Baltimore)* Vol. 79, pp. 369-378.
- Yale S, & Limper A. (1996). Pneumocystis carinii pneumonia in patients without human immunodeficiency syndrome: associated illness and prior corticosteroid therapy. *Mayo Clin Proc*, Vol.71, pp. 5-13
- Yamada R, Suzuki A, Chang X, & Yamamoto K. (2005). Citrullinated proteins in rheumatoid arthritis. *Front Biosci*, Vol. 10, pp. 54-64.
- Yoshinouchi T, Ohtsuki Y, Fujita J, Yamadori I, Bandoh S, Ishida T, & Ueda R. (2005). Nonspecific interstitial pneumonia pattern as pulmonary involvement of rheumatoid arthritis. *Rheumatol Int*, Vol. 26, pp. 121-125

- Zamora AC, Wolters PJ, Collard HR, Connolly MK, Elicker BM, Webb WR, King TE Jr, Golden JA (2008). Use of mycophenolate mofetil to treat scleroderma-associated interstitial lung Disease. *Respir Med*, Vol. 102, pp.150-155.
- Zanelli E, Breedveld FC, & de Vries RR. (2000). HLA class II association with rheumatoid arthritis: facts and interpretations. *Hum Immunol*, Vol. 61, pp. 1254-1261.
- Zhang D & Liu Y. (2010). Surgical Lung Biopsies in 418 Patients with Suspected Interstitial Lung Disease in China. *Inter Med*, Vol. 49, pp. 1097-1102

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Rheumatology is a subspecialty of medicine that focuses on the biology, cause, diagnosis and the treatment of a variety of musculoskeletal and other systemic diseases. The field of rheumatology is expanding rapidly and several very exciting developments have occurred during the recent years. Firstly, there has been a new dramatic understanding of the nature of inflammation and the possibility of specifically regulating the aberrant immune inflammatory response. Secondly, an understanding of pathogenesis has led to the development of new, more targeted therapies. Challenges in Rheumatology has assembled an impressive group of international experts who have studied specific aspects of certain rheumatic diseases and have extensive experience either in pathophysiology, or with the in-depth diagnosis and/or management of rheumatic patients. They communicate their knowledge and experience to the reader in chapters that are conveniently organized as pathophysiology, clinical manifestations and diagnosis of selected rheumatic diseases, medical and perioperative orthopedic management, and the economic impact of rheumatic diseases. We hope that this book will help trainees become better physicians and scientists, and that it will help practicing rheumatologists to provide better care, and ultimately, improve the quality of life of our patients.

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