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Review of Morphological Changes in Regional Lymph Nodes in Pulmonary Fibrosis

Sharipova Elvina Midatovna, Rakhmatova Markhabo Rasulovna
Bukhara State Medical Institute, Uzbekistan

Abstract: Interstitial lung pathology with various manifestations is currently of interest for discussion and the approach of new methods of prevention and treatment of certain types of pulmonary fibrosis. Of particular interest is the study of their clinical and morphological characteristics to identify different types of fibrotic processes occurring in the lungs. The division of pulmonary fibrosis into multiple forms in the histological classification is due to differences in the mechanisms of its occurrence and course. But changes in the lymph nodes in the fibrotic process of the lung tissue have been poorly studied. In the article, we tried to collect literary data on structural changes in regional lymph nodes that occur against the background of pulmonary fibrosis.

Key words: pulmonary fibrosis, regional lymph nodes, literary data, morphology, histology.

Introduction

In obstructive lung diseases, airway wall layers and associated structural remodeling can be identified and quantified. In malignant lung disease, normal and malignant portions of the central airways, lung parenchyma, lymph nodes, and pleura are distinguished. An increasing number of interstitial lung diseases (ILDs) are being imaged using OCT or CLE. Several structural changes associated with ILDs can be imaged: fibrosis, cellular infiltration, bronchiectasis, cysts, and honeycombing. By visualizing individual malignant cells, CLE has the potential to become a tool for real-time detection of lung cancer. In the future, both techniques could be combined with laser fluorescence tracer detection. [1]

Lymph nodes (LNs) are secondary lymphoid organs located throughout the lymphatic system. They function to filter pathogenic material from the lymphatic fluid to maintain the health of the body. Subcapsular sinus macrophages are among the first to respond to LNs due to their strategic location in the subcapsular sinus region. These macrophages facilitate the delivery of immune complexes to B cells and follicular dendritic cells within the LNs .[2]

A precise knowledge of the normal anatomy of the lymphatic system is essential to understand the structural changes that occur in patients with lymphedema. In this article, the authors first review previous anatomical studies and summarize the general anatomy of the lymphatic system and lymphatic pathways in the upper and lower extremities. Second, they present their new anatomical concept of the “lymphosome,” which describes how lymphatic vessels in a given area connect to the same subset of regional lymph nodes .

With the advent of sentinel node technology, many patients now have the option of histopathological diagnosis using lymphatic mapping and selective lymphadenectomy. The detection of sentinel lymph nodes has become an ideal application for nuclear medicine, since anatomical data do not allow us to reflect the close relationships between the lymphatic system and regional lymph nodes or, more specifically, to identify the first draining lymph node .[3]

The lymphatic vasculature maintains tissue homeostasis through fluid drainage as lymph and immune surveillance via leukocyte migration through the lymphatic vessels to the draining lymph nodes. Lymphatic endothelial cells form the lymphatic vessels and sinuses of the lymph nodes and play a key role in the formation of the immune response and tolerance. In the healthy lung, the vast majority of

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lymphatic vessels are located along the bronchovascular structures, in the interlobular septa and in the subpleural space. Recent studies have pointed to the causal role of lymphatic dysfunction in the initiation and progression of lung diseases, indicating that these vessels may be active participants in pathological processes in the lungs. However, the mechanisms of pathogenesis of disorders of the lymphatic function of the lungs are poorly understood, which leaves many unanswered questions .

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first emerged in December 2019 in Wuhan, China, and has developed into a pandemic. Since angiotensin-converting enzyme 2 (ACE2) is one of the potential target receptors of SARS-CoV-2 in the human body, which is expressed in various tissues, multiple organs may be affected. In a study, various organs including lung, gastrointestinal tract, liver, kidney, skin, heart, blood, spleen, lymph nodes, brain, blood vessels, and placenta were carefully examined for pathological changes associated with COVID-19 . The coronavirus disease 2019 (COVID 19) pandemic caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has had a profound impact on global health. SARS-CoV-2 infection primarily affects the respiratory system. With the advent of effective vaccines and treatments against COVID-19, it is now important to better understand the long-term consequences of SARS-CoV-2 infection in order to identify COVID-19 survivors who are at risk of developing chronic pulmonary fibrosis and develop effective anti-fibrotic therapies .[4]

Pulmonary fibrosis is one of the major long-term complications in COVID-19 patients. In addition, risk factors such as advanced age with limited lung function, pre-existing comorbidities such as diabetes, cardiovascular disease, hypertension, and obesity increase the risk of developing pulmonary fibrotic changes in survivors who have reduced exercise capacity.

Important findings include the presence of thrombosis and microangiopathy in small vessels and capillaries of the lungs with associated bleeding, which significantly contributed to death. Evidence of diffuse alveolar damage, including hyaline membranes, was present even in patients not on mechanical ventilation. Cardiac findings included single cell necrosis without lymphocytic myocarditis. No evidence of secondary pulmonary infection caused by microorganisms was found .

The process of fibrogenesis in response to injury is realized through complex cellular interactions in which certain molecular pathways are important .[5]

Idiopathic pulmonary fibrosis (IPF) is a worldwide widespread progressive disease with limited treatment options and poor prognosis. Due to irreversible disease progression, IPF affects the quality and life expectancy of patients and places a significant burden on their families and social health services .

In 5% of cases, idiopathic pulmonary fibrosis occurs with exacerbation. These circumstances have necessitated the development and validation of not only IPF-specific diagnostic biomarkers, but also prognostic biomarkers for the treatment of patients to adopt treatment tactics, including lung transplantation. Recent advances in considering several biological pathogenetic pathways combined on the basis of IPF have revealed different molecular phenotypes resulting from a complex interaction of genetic, epigenetic, transcriptional, metabolic and environmental factors.[6]

Idiopathic pulmonary fibrosis stands out as one of the most aggressive forms of interstitial lung diseases, currently not amenable to definitive treatment. The authors proposed a clinical assessment based on MDD to predict mortality among these patients .[7]

Interstitial lung diseases are a heterogeneous group of diseases represented mainly by fibrosing alveolitis (pulmonary fibrosis), sarcoidosis, histiocytosis X, and alveolar proteinosis. The feature that unites these nosological forms is the chronic progressive development of pulmonary fibrosis with the formation of respiratory failure .

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The results of a histological study of lung biopsies of patients with interstitial lung diseases determined differences in the localization of pathological processes, the frequency of occurrence and severity of morphological signs reflecting inflammatory and fibrotic changes in the lung parenchyma. The possibility of identifying objective signs for dividing a heterogeneous group of interstitial lung diseases into histological patterns by the type of pulmonary fibrosis justifies the need to focus on the results of a morphological study when choosing treatment tactics for patients and determining the prognosis of the disease.[8]

Patients with clinically overt ILDs, whether associated with CTD or not, may exhibit common clinical features of the disease, which is associated with progressive pulmonary fibrosis. In recent years, the tyrosine kinase inhibitor nintedanib has demonstrated efficacy and safety in idiopathic pulmonary fibrosis. Data from phase II studies also suggest that pirfenidone, which has a different but largely unknown mechanism of action, may also be active in other fibrosing ILDs with a progressive phenotype, in addition to its known efficacy in IPF.

A mouse model of pulmonary fibrosis induced by intratracheal bleomycin (BLM) was established. The researchers found that MCTR1 intervention attenuated the inflammatory and fibrotic response of the lungs induced by BLM. Furthermore, MCTR1 protected BLM-induced epithelial cell destruction and reversed the epithelial-mesenchymal transition phenotype in mice with pulmonary fibrosis. Most importantly, MCTR1 treatment restored BLM-induced lung dysfunction and significantly increased survival . Post-treatment with MCTR1 attenuated BLM-induced inflammation and fibrotic changes in mice, suggesting that MCTR1 may serve as a novel therapeutic strategy for fibrosis-related diseases .

Due to differences in study methodologies, there are variations in the reported incidence and prevalence of IPF worldwide. Based on the countries included in our analysis, we estimated the adjusted incidence and prevalence of IPF to be in the range of 0.09–1.30 and 0.33–4.51 per 10,000 persons, respectively. According to these prevalence estimates, IPF remains a rare disease. To ensure consistency, future epidemiological studies of IPF should consider age, sex, smoking status, and specific case definitions .

Diffuse parenchymal lung diseases encompass a large number of conditions with a wide range of causes, clinical manifestations, imaging and pathologic features, and variable outcomes. Idiopathic pulmonary fibrosis is more common in men than in women (sex ratio 7:3) and is more common in people over 60 years of age than in younger people.1,2 IPF is a chronic and irreversible disease that typically progresses to respiratory failure and death (median interval between diagnosis and death 3 years).3 In contrast to IPF, other ILDs are typically characterized by a younger median age at presentation (20 to 60 years) and a more balanced sex ratio. Pulmonary fibrosis in different disease contexts and entities has been reviewed, highlighting similarities in pathophysiology, clinical manifestations, and diagnostic features, as well as the similar progressive nature of many of these diseases .[9]

Pirfenidone is currently approved in the EU for the treatment of mild to moderate idiopathic pulmonary fibrosis (IPF) and has a favourable risk/benefit profile. However, there are several other progressive fibrotic lung diseases for which conventional anti-inflammatory therapy is insufficiently effective and antifibrotic therapy may offer a new treatment option . We designed a study protocol to include patients with progressive pulmonary fibrosis despite conventional anti-inflammatory therapy. The study population included patients with pulmonary fibrosis associated with collagen vascular disease, fibrotic non-specific interstitial pneumonia, chronic hypersensitivity pneumonitis and asbestos-related pulmonary fibrosis. The absolute change in predicted FVC as a percentage from baseline, analysed using the rank analysis of covariance model, will serve as the primary efficacy endpoint of the study.

Interstitial lung disease associated with systemic sclerosis (SSc-ILD) shares a number of clinical features and pathogenetic mechanisms with idiopathic pulmonary fibrosis (IPF). The aim of this study

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was to evaluate the tolerability of pirfenidone in the treatment of IPF in SSc-ILD. The known adverse events (AEs) of pirfenidone from the gastrointestinal tract, skin and liver are important given the involvement of these organs in the development of SSc. Pirfenidone showed an acceptable tolerability profile in SSc-ILD, although longer titration may be associated with better tolerability. Concomitant use of MMF did not affect tolerability. The obtained results support further study of pirfenidone in future clinical trials in patients with SSc-ILD.

Mediastinal lymph node enlargement on chest CT is common in patients with interstitial lung disease and may reflect immunologic activation and subsequent cytokine-mediated immune cell trafficking.

We aimed to determine whether increased MLN on chest CT predicts clinical outcome and circulating cytokine levels in ILD. The results of this study showed that increased MLN predicts TFS and hospitalization risk in ILD and is associated with decreased levels of a key circulating cytokine, soluble CD40L. Incorporation of MLN and cytokine data into current prediction models may improve ILD prediction.

Another study analyzed data from 676 patients with FBL, age 53.3±15.2 years (f/m - 412/264). This was done to assess the changes in the radiological and morphological picture of fibrosing pulmonary diseases (FLD) during their long-term observation. HRCT, SPECT, KIFVD (with DSL), echocardiography were performed. Early signs of FLD in 32 patients (4.7%, DSL 70% of D) on CT, SPECT and morphology were manifested by minimal changes, transformed into a picture of FLD in 21 patients .

A recent study included patients with IPF from the Interstitial Lung Disease Registry at Seoul National University Bundang Hospital from January 2012 to March 2016. Two thoracic radiologists independently examined the mediastinal LNE, lung parenchymal fibrosis, and ground- glass opacities on the chest CT scan of each patient, which were obtained at diagnosis. Mortality and hospitalization rates were analyzed .

Lung tissue in chronic renal failure, macroscopic analysis, study of morphological changes. The study used 150 laboratory white mice, male and female, aged 5, 9, 12 months, which were divided into 3 groups (n = 50 in each) depending on the observation period. In the experiment, they were intramuscularly administered 5%-0.8 mg/100 mg glycerol for one month to induce chronic renal failure. On the 30th day of observation, massive focal and total hemorrhages, typical signs of emphysema, were observed in macroscopic preparations of lungs isolated from mice . This study included patients with idiopathic pulmonary fibrosis (IPF) or non-specific interstitial pneumonia (NSIP) from January 2009 to December 2018. Two radiologists independently assessed the diameter and location of MLNs. Patients with ILD associated with drug toxicity, sarcoidosis, chronic hypersensitivity pneumonitis, and other rare idiopathic interstitial pneumonias were excluded. The primary endpoint was survival. Secondary endpoints included the number of respiratory-related hospitalizations, lung function assessed by forced vital capacity and diffusing capacity of carbon monoxide (DLCO), and pulmonary fibrosis score determined by computed tomography .

In patients with IPF and NSIP, increased MLN predicts survival, is associated with increased hospitalizations, and demonstrates signs of worsening lung function and more severe fibrosis .

The aim of this study was to determine the incidence, clinical, and morphological features of mediastinal lymphadenopathy (MLN) in patients with pulmonary sarcoidosis (PS), disseminated pulmonary tuberculosis (DPT), and exogenous allergic alveolitis (EAA). Thus, MLN is observed in all studied granulomatous lung diseases, but the frequency and severity of its expression, the composition of the involved groups of IMLNs, and the nature of morphological changes are different, which can be used in diagnostics .

There are experimental models of pulmonary fibrosis development. The problem of creating an

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effective experimental model of pneumosclerosis is due to the variety of etiological factors and the heterogeneity of this disease. The development of the disease is facilitated by various factors and pathogenetic pathways that influence the formation of chronic inflammation, damage to small bronchi, destruction of the pulmonary parenchyma and the vascular system of the pulmonary circulation . Nitrogen oxides play an important role in the development of environmentally conditioned lung diseases (chronic obstructive pulmonary disease, bronchial asthma, pulmonary interstitial fibrosis), initiating damage and death of bronchoalveolar epithelial cells. One of the most aggressive anthropogenic pollutants is nitrogen dioxide (NO2), the content of which in the atmosphere of megalopolises can exceed hygienic standards by tens of times. The main source of NO2 is emissions from motor vehicles, power plants and boiler houses (during combustion of organic fuel), chemical and metallurgical enterprises .

Mediastinal lymph node enlargement is prevalent in patients with idiopathic pulmonary fibrosis (IPF). The expression of programmed cell death-1 (PD-1)/programmed cell death ligand- 1 (PD-L1) in mediastinal lymph nodes and lung tissues was analyzed. PD-1, PD-L1 mRNA expression was measured in tracheobronchial lymph nodes of mice after bleomycin-induced injury on day 14. Finally, the effect of PD-1 inhibitor, pembrolizumab, on bleomycin-induced pulmonary fibrosis was investigated.[10]

Mediastinal lymph nodes of IPF patients exhibit different expression profiles than those of lung cancer patients, indicating different immune-mediated pathways regulating fibrogenesis and carcinogenesis. PD-1 expression in mediastinal lymph nodes is consistent with that in lung tissue. Lower doses of pembrolizumab may have antifibrotic effects.

Conclusions

Structural changes in regional lymph nodes during inflammation in the region are determined by the level of development and activity of the inflammatory reaction, includes a wide range of alterations, a decrease in the immune reproductive function, but with the preservation of the barrier. A decrease in the activity of the inflammatory reaction in the region, in accordance with this, a decrease in the toxic effect of the region is accompanied by a rapid restoration of the structural organization of the lymph nodes.

In general, the study of available literary data revealed a lack of information on the effect of pulmonary fibrosis on the structural and morphological state of the tissue of regional lymph nodes.

The poor study of this problem makes it possible to further study it and search for new methods of treatment, as well as the development of new drugs to correct these changes.

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