Prevalence of bronchiolitis in patients with Rheumatoid arthritis

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Abstract: Inflammation of the bronchioles is common in various diseases. The cause of the pathological process in the bronchioles are respiratory diseases, COPD, bronchial asthma, damage to the respiratory tract by toxic substances. Bronchiolitis is a heterogeneous group of diseases that are less common than obstructive pulmonary disease or asthma, and are a manifestation of nonspecific reactions of lung tissue to damaging factors. The most common form of the disease is unilateral focal bronchiolitis. Unilateral bronchiolitis has a more favorable prognosis than the bilateral variant. Bilateral bronchiolitis often leads to the development of cardiopulmonary insufficiency. The diagnosis of the disease is carried out by examining the function of external respiration, bronchoscopy, bronchography, advanced computed tomography of the chest organs. Although the first description of bronchiolitis was made back in 1901 by V. Lange, the diagnosis and treatment of bronchiolitis remains a difficult task, perhaps because bronchiolitis is much less common compared to COPD or BA. Rheumatoid arthritis (RA) is one of the most common rheumatic diseases, affecting up to 1% of the adult population in the developed countries of the world. Little is known about the frequency of bronchiolitis in RA patients. The first descriptions of RA-associated bronchiolitis (RB) referred to isolated severe, rapidly progressive, often fatal cases. Respiratory organ damage (OD) is one of the most frequent extra-articular manifestations of rheumatoid arthritis (RA), which, according to some data, develops in 60-80% of patients with RA (Cortet B. et al., 1997; Turesson C. et al., 2003). The lesion associated with RA can occur at any level and with the involvement of almost all structures of the respiratory system: respiratory tract, lung parenchyma, serous membrane (Suda T., 2015), at the same time, the lesion pulmonary vessels are an extremely rare phenomenon (Fischer A., du Bois R., 2012).

Keywords: rheumatoid arthritis, bronchiolitis, bronchial obstruction, multispiral computed tomography

INTRODUCTION

As is known, bronchioles are the most distal branches of the bronchi with a diameter of 2 mm or less, which do not contain cartilage elements in their wall. In clinical practice, bronchiole lesions are not uncommon and can be a manifestation of a number of pathological processes. These include infections, rheumatic diseases, most often rheumatoid arthritis (RA), post-transplant complications, toxic effects of drugs, as well as conditions caused by inhalation of irritating gases and vapors. Various options the inflammatory process at this level of the lower respiratory tract (NDP) is often referred to by the generalizing term "bronchiolitis". The literature cited mortality rates from RB up to 50% during the year. Later it became clear that the course of RB is variable in the severity of symptoms and the rate of progression of irreversible changes in the lungs, and in a significant number of patients the deterioration is slow. It was suggested that many patients there are rarely diagnosed subclinical manifestations of RB. However, systematic data on the prevalence of RB have been absent for a long time. In a continuous prospective examination of 104 non-smoking RA patients using multispiral computed tomography (CT) of the lungs - the most sensitive of the instrumental methods for diagnosing distal bronchial lesions - direct and indirect radiological signs of bronchiolitis were detected in different combinations in 36 (35%) RA patients compared with 1 (2%) by a patient of the control group (in control there were no RA and chronic respiratory diseases. Accordingly, the prevalence of RB diagnosed by CT signs of distal bronchial lesions can reach 350 per 1000 non-smoking RA patients. These results force us to reconsider the point of view of RB as a rare and unambiguously prognostically unfavorable variant of lesion NDP in RA patients. Before the advent of lung MSCT, descriptions of bronchiolitis in RA patients were devoted to isolated cases of fulminant course of this lesion with severe irreversible bronchial obstruction (BO), increasing shortness of breath and, as a rule, poor outcome [3-4]. However, the data obtained using new NDP imaging methods suggest a greater prevalence and a wide range of severity of bronchiolitis in RA patients than previously thought. The emergence of new instrumental research methods, including multispiral computed tomography of the lungs (MSCT), expanded the possibilities of lifetime diagnosis of low-symptomatic lung lesions and PDP in patients with cancer and allowed a new look at the epidemiology, clinical features and diagnosis of the latter. The above fully applies to the lesion of the distal parts of the bronchial tree - bronchiolitis.

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The aim of this study was to clarify the prevalence and clinical picture of lesions of the distal bronchial tree (bronchiolitis) in RA patients.

MATERIALS AND METHODS

52 patients (7 men and 45 women) with a reliable diagnosis of RA were examined based on the criteria of the American College of Rheumatologists in 1987. Sr. the age of patients was 55.8 ± 14.7 years. The average duration of the disease is 12.4 ± 8.6 years. Seropositive according to the RF RA - 52 (75%) patients. RA activity according to the DAS28 index is ≈ 5.5 ± 1.4 (2.0 - 7.9) points. The control group consisted of 50 patients (11 male and 39 female) aged 52.9 ± 14.4 years, who had no signs of RA. The group of examined persons (RA patients and control group patients) did not include smokers and patients with chronic respiratory diseases, acute and chronic heart failure, blood diseases, acute and chronic renal failure.

In RA patients and control group patients, general clinical examination, spirometry, bodyplethysmography, study of lung diffusion capacity (DSL), multispiral computed tomography (MSCT) of the lungs were performed.

RESULTS

Clinical, functional and/or CT-signs of NDP lesion were detected in 32 (62%) RA patients. Shortness of breath during exercise was observed in 27 (52%) patients. In 8 (15%) patients, there was a chronic (i.e., observed for most days, at least three months a year, for at least two years in a row) cough. In 7 (13.5) cases, it was accompanied by the separation of mucosal or mucopurulent sputum. Periodic breathing difficulties were noted by 11 RA patients (21.1%). In the control group, chronic productive cough occurred in 2 (4%) patients ($p < 0.01$), dyspnea - in 5 (9%) ($p < 0.01$), patients of the control group did not complain of difficulty breathing ($p < 0.01$).

In the study of the function of external respiration (FVD), not completely reversible generalized bronchial obstruction (BO) was detected in 9 (17.3%) patients with RA. Another 13 (25%) patients had a distal variant of BO (violation of patency of small bronchi). No cases of generalized BO were detected in patients of the control group ($p < 0.01$), the distal variant of BO was found in 5 patients (9%) ($p < 0.01$).

Direct (centrilobular micro-foci, structures of the "tree with kidneys" type) and indirect signs of bronchiolitis (areas of "mosaic perfusion", the phenomenon of "air trap") in various combinations were detected with lung MSCT in 35% of RA patients ($n = 18$) and 2% ($n = 1$) of control group patients ($p < 0.01$).

Patients with CT signs of bronchiolitis often complained of shortness of breath (69% of cases, n =25), cough (56%, n = 10), sputum separation (56%, n = 10), less

often - for a periodic feeling of difficulty breathing (25% of cases, n = 5) (Table 1). However, these complaints were not specific to persons with distal bronchial lesions and did not they allowed us to confidently distinguish them from the general group of RA patients. The nature and frequency of respiratory symptoms in RA patients with the presence and absence of CT-signs of bronchiolitis did not differ significantly.

The results of lung MSCT in RA patients allow us to consider the proximal lesion as a probable cause of cough and sputum production in patients without signs

of bronchiolitis NDP. Signs of deforming proximal bronchitis were detected in 38% of patients in this group. The high frequency of concomitant lesions of the proximal bronchi was also characteristic of patients with CT signs of bronchiolitis. Almost all of them (n = 34, 94%) had a thickening of the wall of the visible bronchi or the formation of BE. Availability structural changes in the large bronchi in patients with bronchiolitis phenomena suggest that in RA, the lesion of the bronchioles is not anatomically isolated. Apparently, bronchiolitis in RA patients is part of a diffuse inflammatory-sclerotic lesion NDP (obstructive deforming rheumatoid panbronchitis), the consequences of which are thickening of the walls and deformation of the lumen of large bronchi, the formation of EB and constriction of bronchioles with the gradual formation of a poorly reversible BO.

Auscultative symptoms in RA patients with bronchiolitis were poor. Only one patient with a histologically verified diagnosis of constrictive bronchiolitis with lung auscultation had dry and crepitating wet wheezes without significant changes in percussion sound. Perhaps the scarcity of auscultative symptoms is a feature of rheumatoid bronchiolitis, although the literature descriptions of this variant of NDP lesions in RA mention the presence of wet wheezing in the lungs in patients. Little-reversible BO was detected in 5 (28%) patients RA with a picture of bronchiolitis, including moderately severe, severe and extremely severe BO (FEV1 < 60% of the proper value) - in 3 patients (17%). In patients without signs of damage to the distal bronchi, BO was detected in 5 (13%) cases. The distal variant of BO was present in 5 RA patients with CT signs of bronchiolitis. In total, obstructive pulmonary ventilation disorders were detected in 9 (53%) RA patients with bronchiolitis. Patients with lesions of the distal bronchi had lower rates of forced expiratory volume in 1 s (FEV1) (84.0 ± 31.7% vs. 99.1 ± 17.5% in persons without bronchiolitis, $p < 0.05$). The degree of reduction of FEV1 in patients with no symptoms of bronchiolitis was minimal (FEV1 ≥ 70% of the due in all cases). Severe ventilation disorders were present only in patients RA with damage to the distal bronchi. Thus, the addition of bronchiolitis can be considered.

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Restrictive disorders of pulmonary function were detected in 2 (8%) RA patients with bronchiolitis (total lung capacity - OEL - 61.5 ± 9.4%). At the same time, all these patients had a decrease in DSL (carbon monoxide transfer factor (II), DL, CO = 60.0 = 14.0%). In RA patients without damage to the distal bronchi, restrictive changes were detected in 8 (12%) cases, a decrease in DSL was also noted in 8 (12%) cases.

With MSCT of the lungs in RA patients with bronchiolitis, restriction and a decrease in DSL, changes in the type of interstitial pulmonary fibrosis (linear cords, reticulation, changes in the broncho-vascular architectonics of the lungs of varying severity), as well as signs of damage to the proximal bronchi, were determined. This suggests that these patients have simultaneous multilevel damage to the respiratory organs: bronchial tree throughout and interstitial lung.

The results obtained indicate the prevalence of a low-symptomatic course of bronchopulmonary lesions in RA patients. In 5 (31%) patients with RA with a CT picture of bronchiolitis, clinical manifestations from the respiratory organs were not detected, in another 5 (28%) they were minimal - periodic cough, slight shortness of breath during exercise (not higher than grade 1 by MRC) and/or changes in pulmonary function by the type of distal sulcus.

Morphological interpretation of distal bronchial lesions in RA patients was possible in one of the cases we observed. Microscopic examination of a lung tissue biopsy in a 45-year-old RA patient with an unproductive cough, progressive shortness of breath, severe The presence of chronic constrictive bronchiolitis and signs of damage to the distal parts of the bronchial tree according to the MSCT of the lungs (centrilobular foci, the symptom of a "tree with kidneys", the phenomenon of an "air trap") showed the presence of chronic constrictive bronchiolitis (Fig. 3). This histological variant of bronchiolitis is considered the most common in patients with RA.

The results of this study do not provide grounds for the association of cases of bronchiolitis in RA patients with the activity of the underlying disease and the use of disease-modifying agents of various groups.

Due to the prevalence of multilevel lung damage and PDP in RA patients, it turned out to be difficult to identify and describe the "clinical image" of bronchiolitis. The frequent low-symptomatic course and the nonspecificity of respiratory complaints present in patients bring to the fore in the diagnosis of distal bronchial lesions in RA patients a combination of functional (examination of pulmonary flows and volumes) and X-ray (lung MSCT) methods. The study of pulmonary function today forms the basis for the diagnosis of bronchoobstructive diseases, and the importance of its regular implementation in patients with RA, due to the high risk of joining BO, it is obvious. Lung MSCT, in turn, is the most sensitive of the instrumental methods for diagnosing PDP lesions and the only non-invasive method for detecting bronchiolitis in RA patient. MSCT it also allows to identify concomitant lesion of the interstitium and parenchyma of the lungs and provides important information to exclude or confirm other lung diseases with which a differential diagnosis will be required. Implementation of a full-fledged primary diagnosis of NDP lesions in patients RA without MSCT of the lungs seems impossible today. The results of this study force us to reconsider the point of view of bronchiolitis as a rare and prognostically unfavorable bronchopulmonary manifestation in RA patients. Based on lung MSCT data, bronchiolitis could be diagnosed in 18 (35%) of the 52 RA patients we examined. Accordingly, the prevalence of this variant of bronchopulmonary lesions can reach 350: 1000 non-smoking patients.

A generally accepted approach to the treatment of bronchiolitis in RA patients has not been formed to date. With non-infectious lesions of the distal bronchi, immunosuppressive and symptomatic therapy is traditionally resorted to. In the patients we observed, inhaled bronchodilators (β2-agonists and long - and short-acting M-cholinolytics) were successfully used against the background of ongoing basic anti-inflammatory therapy. In case of constrictive bronchiolitis of severe progressive course within the framework of RA, satisfactory the effect (stabilization of FVD indicators, a significant decrease in the severity of cough and shortness of breath) was obtained by us against the background of combined immunotherapy with nosuppressive therapy according to the scheme: azathioprine 100mg/day + methylprednisolone 12 mg/day + budesonide1000 mcg / day by inhalation through a nebulizer, in combination with the inhalation use of bronchodilators. In recent years, encouraging data have been obtained on the successful use of azithromycin and other macrolide antibiotics in distal bronchial lesions of various (including non-infectious) etiologies. The effectiveness of inhalation forms is being studied cyclosporine A and various biological agents. However, the optimal schemes of drug treatment of

bronchiolitis in RA patients, indications for its active treatment and the prognostic value of both rheumatoid bronchiolitis itself and various variants of its drug therapy should be clarified in further studies.

CONCLUSION

Bronchiolitis is a common variant of NDP lesion in RA patients. In patients with CT signs of bronchiolitis, cough, sputum production, shortness of breath, and a feeling of difficulty breathing are often detected. Obstructive pulmonary function disorders are characteristic, some patients retain normal lung function parameters or there is restriction. In patients with RA, low-symptomatic forms of distal bronchial lesions are common.

Manifestations of bronchiolitis are naturally combined in RA patients with signs of involvement of the proximal bronchi, and can also be detected in persons with a symptom complex of interstitial lung damage.

Due to the non-specificity of clinical manifestations of bronchiolitis and the multilevel nature of respiratory damage in RA patients, MSCT plays a major role in the diagnosis of bronchiolitis. When using this method, signs of damage to the distal parts of the bronchial tree are detected in 35% of patients.

In RA patients with progressive bronchiolitis, stabilization of indicators is possible

FVD and improvement of well-being against the background of immunosuppressive and broncholytic therapy.

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