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PULMONARY INVOLVEMENT IN SYSTEMIC LUPUS ERYTHEMATOSUS

***[1]Artur Zoto, [2]Hasan Hafizi, [3]Renato Osmenaj, [4]Elvis Pavli, [5]Brikena Selimi**

[1]Department of Rheumatology, University Hospital Center "Mother Teresa", Tirana, Albania
[2]Department of Lung Diseases, University Hospital of Lung Diseases "Shefqet Ndroqi", Tirana, Albania
[3]Department of Radiology, University Hospital Center "Mother Teresa", Tirana, Albania
[4]Department of Cardiology, University Hospital Center "Mother Teresa", Tirana, Albania
[5]Department of Ophthalmology, University Hospital Center "Mother Teresa", Tirana, Albania

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ABSTRACT

Objective. The aim of this study was the identification of pulmonary manifestations in patients with systemic lupus erythematosus and their assessment in relation to immunological alterations.
Methods. This is a cross-sectional study that analyzed 90 patients with systemic lupus erythematosus. Patients were examined by laboratory tests such as: anti-nuclear antibody, anti double stranded deoxyribonucleic acid antibody, anticardiolipin antibodies and D dimer. Pulmonary high-resolution computed tomography, computerized tomographic pulmonary angiography, pulmonary function tests and echocardiography doppler were performed for the patients.
Results. Pleural effusion were 26 (28.9 %) patients. Interstitial lung disease were 9 (10 %) patients, acute lupus pneumonitis 2 (2.2 %) patients, pulmonary embolism 10 (11.1 %) patients and pulmonary arterial hypertension were 6 (6.7 %) patients. Restrictive ventilator insufficiency are 27 (30 %) patients.
Conclusions. Pulmonary manifestations are common in systemic lupus erythematosus and have a wide spectrum. These injuries are anatomical and functional. Immunological alterations are important factors in pulmonary injuries.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a complex systemic autoimmune disease, with numerous immunologic and clinical manifestations (Capobianco *et al*, 2012). It is considered as the prototype of autoimmune disease and it is characterized by the production of a wide series of autoantibodies as well as by a variable clinical presentation (Ferreiro *et al*, 2011). Clinically characterized by multisystem involvement and varied serologic abnormalities, no two patients present or have disease that evolves in exactly the same way (Swigris *et al* 2008). More than half of all patients with SLE will experience involvement of the lung parenchyma, pulmonary vasculature, pleura, or chest wall, which are collectively considered pulmonary manifestations of lupus (Paran *et al*., 2004; Keane *et al*, 2000; Kim *et al*, 2000). The prevalence of respiratory manifestations in patients with systemic lupus erythematosus varies depending on several factors, including methods of diagnosis, time of follow-up, etc (Pego-Reigosa *et al*, 2009). The aim of this study was the identification of pulmonary involvement in patients with SLE, their assessment in relation to immunological alterations.

Corresponding author: Artur Zoto
Department of Rheumatology, University Hospital Center "Mother Teresa", Tirana, Albania

MATERIALS AND METHODS

Patients

Inclusion criteria

This is a cross-sectional study that analyzed 90 patients with systemic lupus erythematosus. These patients were hospitalized in the clinic of Rheumatology, Lung diseases or followed as outpatients. All patients fulfilled the criteria of the American College of Rheumatology for the diagnosis of SLE (Hochberg, 1997). Exclusion criteria Lupus patients who have suffered in the past or were actually suffering from other diseases (e.g. sarcoidosis, tuberculosis, emphysema, congestive heart failure, congenital heart disease, cirrhosis of

the liver) which may influence the pulmonary injuries, smoking patients, pregnant women and those breastfeeding, and also patients with a history of any occupational exposure to inorganic or organic dusts (e.g.asbestosis, silicosis) or drug-induced lupus were excluded from the study.

The examinations

Patients were examined by laboratory tests tests such as: anti-nuclear antibody (ANA), anti double stranded deoxyribonucleic acid antibody (anti-dsDNA) and anticardiolipin antibodies (aCL) IgG, IgM, D dimer. Patients were examined with high resolution computed tomography (HRCT) and in patients with clinical and laboratory suspicion of pulmonary embolism was used computerized tomographic pulmonary angiography (CTPA). HRCT and CTPA findings were recorded in consultation with the radiologist. Patients were examined with transthoracic Doppler echocardiography for pulmonary arterial hypertension (PAH) and were referred to the cardiologist for interpretation of the related findings. Lung function was measured with spirometry.

The Interpretation of findings

Patients were considered to have pleural effusion when they showed in HRCT abnormal collection of fluid in the pleural space. Patients were considered to have interstitial lung disease (ILD) when they showed HRCT of the lung findings compatible with ILD such as: nodular, reticular, reticulonodular, ground-glass opacities, honeycombing, dominantly on lung bases. ILD diagnostic criteria for this study were defined according to American Thoracic Society / European Respiratory Society International Multidisciplinary Consensus Classification of idiopathic interstitial pneumonias (Travis *et al*, 2002). In acut lupus pneumonitis (ALP) radiographic findings include bilateral alveolar infiltrates with predominance in lower lung fields. Pulmonary embolism, riding embolus in the pulmonary trunk and in both pulmonary arteries and in smaller branches bilaterally as well. Contrast filling defects are seen according to the emboli. Diagnostic criteria for pulmonary embolism were defined according guidelines on the diagnosis and management of acute pulmonary embolism (Torbicki *et al*, 2008).

The systolic pressure in the pulmonary artery was evaluated based on tricuspid regurgitation peak flow velocity m/ s using the Bernoulli equation 4 x (tricuspid regurgitation jet)2 + right atrial pressure of 5 mm/hg. The value of pulmonary artery systolic pressure (PASP) >36 mm/ hg was considered as PAH (Galie *et al*, 2009). Indicators of pulmonary function included forced vital capacity (FVC), forced expiratory volume in the first, second (FEV1), and FEV1/FVC ratio. Based on the American Thoracic Society criteria, patients with normal FEV1/ FVC ratio and decreased FVC <80% were diagnosed as having restrictive disease (Miller *et al*, 2005). These data were expressed as percentages of the predicted values, based on patient s sex, age, height and weight. To determine if immunological alterations are associated with pulmonary injury, patients are classified into two groups. The first group included patients with positive ANA, anti-dsDNA and aCL; the second group included patients with antinuclear antibodies (ANA) negative, anti-dsDNA and aCL negative.

Statistical analysis

Continuous variables were expressed as mean values and their respective standard deviations. Categorical variables were presented in absolute values and their respective percentages. Differences between the categorical variables were assessed with Chi square test. The P value ≤ 0,05 was considered a statistically significant. Odds ratio and 95% confidence interval (95% CI) were used to compare the risk of pulmonary involvement in patients with alteration of immunologic examination. Data were analyzed using the Statistical Package for the Social Sciences (SPSS) software, version 19.0.

RESULTS

The mean (±SD) age of the patients was 37.15±11.41. The mean (±SD) duration of disease was. 6.48±3.89. Female patients were 78 (86.6%) and 12 (13.3 %) patients were males. ANA positive are 84 (93.3%) patients, anti-dsDNA positive are 58 (64.4%), aCL positive are 22 (24.4%) patients. Pleural effusion were 26 (28.9 %) patients, ILD is identified in 9 (10 %) patients, acute lupus pneumonitis 2 (2.2 %) patients, pulmonary embolism 10 (11.1 %) patients and pulmonary arterial hypertension 6 (6.7 %) patients (Table 1). Pleural effusion is significant versus others pulmonary manifestations p < 0,001 (table 1). Pulmonary function abnormalities are 27 (30 %) patients and all have restrictive ventilator insufficiency. In patients with positive ANA , anti-dsDNA and aCL were 84 (100.0 %) of whom 52 (61.9 %) represent pulmonary injury (group 1), while in the other group (group 2) of 6 (100.0 %) patients who do not have positive ANA, anti-dsDNA and aCL only 1 (16.7 %) patients have pulmonary injury (Table 2). Pulmonary involvement in patients with positive immunological tests are significant versus patients with negative immunological tests p=0.03 (Table 2). Patients with alterations of immunological tests have 8.13 times more likely to have lung injuries compared to patients without alterations of immunological tests (OR=8.13, 95% C.I. = 1.09 to 60.53).

Table 1. Pulmonary manifestations in SLE

Condition	Number of patients	Percentage	P-value
Pleural effusion	26	28.9*	< 0.001
Interstitial lung disease	9	10.0	
Acut lupus pneumonitis	2	2.2	
Pulmonary embolism	10	11.1	
Pulmonary hypertension	6	6.7	
Normal	37	41.1	
Total	90	100.0	

* Percentage among the total number of patients (N=90).

Table 2. Pulmonary injuries by immunological alterations

Patients' group	Total	No pulmonary injury	Pulmonary injury	P-value
Group 1	84 (100.0)	32 (38.1)*	52 (61.9)	= 0.03
Group 2	6 (100.0)	5 (83.3)	1 (16.7)	

*Absolute numbers and row percentage (in parentheses).

DISCUSSION

Pleuropulmonary manifestations in this study were found in 59 % of patients and our opinion indicates that pulmonary injuries are important manifestations of SLE. Pleuropulmonary

involvement occurs in approximately 50%–60% of patient in another study (Kim *et al*, 2002). Pleural effusion, ILD, acute lupus pneumonitis, pulmonary hypertension and pulmonary trombosis are injuries that are found in these patients predominantly pleural efussion. This injury is found in 29 % patients. Others autors show that pleural disease is the most frequent respiratory manifestation, and pleural effusions are found in 30%–50% of patients with systemic lupus erythematosus during the course of the disease (Capobianco *et al*, 2012). Clinically apparent effusions have been reported in up to 50% of patients and pathological involvement at autopsy in up to 93% of patients (Crestani, 2005). Chronic ILD is reported in a variable number of patients with SLE. ILD in this study is found in 10 % of patients. ILD or chronic pneumonitis in SLE occurs in 3 to 8% of patients (Hochberg, 1997). Using only imaging criteria, the frequency is higher, between 6 and 24% on the chest radiograph and can reach 70% on CT scans (Fenlon *et al*, 1996; Gaude *et al*, 2009). The onset of ILD is often insidious, but it can also occur after an episode of acute pneumonitis (Pego-Reigosa *et al*, 2009).

Acute lupus pneumonitis (ALP) is an uncommon manifestation of SLE, occurring in 1–4 % of patients (Orens *et al*, 1994). Acute lupus pneumonitis has been very widely described, but in reality its frequency does not exceed 4% of cohorts (Kim *et al*, 2002; Orens *et al*, 1994). In our study, lupus pneumonitis were found in 2 % patients. Pulmonary vascular involvement in lupus is also observed in our study such as pulmonary tromboemboli and pulmonary hypertension. PAH in patients with SLE and antiphospholipid antibodies has been reported and described in different frequencies. The prevalence of PAH in SLE is estimated to be between 0,5-43 % or 2,8 -14 % in others studies (Johnson *et al*, 2004; Humbert *et al*, 2006; Pan *et al*, 2000). This PAH is usually primary but may be secondary to recurrent thromboemboli, a complication of interstitial lung disease or a feature of SLE mixed connective tissue disease overlap syndrome (Carmier *et al*, 2010; Rockall *et al* 2001). In our study were found PAH in 7 % patients and PAH is primary. Pulmonary embolism occurs in up to 25% of patients with SLE and it is an important cause of death (Gladman *et al*, 1980; Pines *et al*, 1985). Anticardiopin antibodies of the IgG or the IgM isotype are found in 13 and 24 % of the patients with SLE, and are associated with an increased prevalence of thrombosis (Cervera *et al*, 1993).

In this study were found pulmonary embolism in 11 % of patients. PFT abnormalities in patients with SLE are common and PFTs typically reveal a restrictive lung physiology (Nakano *et al*, 2002; Ramirez MP *et al*. 2011). Pulmonary function tests were abnormal in about 50% of the patients with nonspecific interstitial pneumonia (NSIP) in SLE is not well defined (Tansey *et al*, 2004). Pulmonary function abnormalities were reported in 41% patients in other study (Kamen DL *et al*, 2010). In this study PFT abnormalities are found in 30 % of patients. Pulmonary function test demonstrates restrictive ventilatory defect in all patients and restrictive defect occurs due to ILD and pleuritis. According to this study in patients with ANA positive, anti-dsDNA positive, aCL positive pulmonary injury occurred frequently in 62 % patients and we found correlation. Tissue damage and dysfunction are mediated by autoantibodies and immune complex formation (Paran *et al*, 2004). Immunologic lung diseases develop when the normal mechanisms of immune self-tolerance fail, macrophages and lymphocytes are the key cells involved in the initiation and perpetuation of the acquired immune response in the lung (Cojocaru *et al*, 2011). Tissue injury appears to be mediated by characteristic autoantibody production, immune complex formation, and their organ-specific deposition. As expected in a multisystem disease, the entire pulmonary system is vulnerable to injury (Cojocaru *et al*, 2011).

Study limitations

The patients in our study were selected from a university hospital, which could potentially be prone to selection bias by including patients with more severe stages of the disease compared to patients at the community level. However, we tried to minimize this bias by recruiting also all the patients from the hospitals outpatient consultation clinics.

Conclusions

Pulmonary manifestations are common in SLE and have a wide spectrum. Pleural involvement, parenchymal disease, pulmonary vascular disease are manifestations than occur in SLE. These injuries are anatomical and functional. Immunological alterations are important factors in pulmonary injuries.

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