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PULMONARY MANIFESTATIONS IN SYSTEMIC LUPUS ERYTHEMATOSUS

Artur Zoto, Hasan Hafizi, Elizana Petrela, Teuta Backa, Renato Osmenaj, Maksim Basho, Zamira Ylli, Edmond Zaimi, Elvis Pavli, Arjan Harxhi

Department of Rheumatology, University Hospital Center "Mother Theresa", Tirana, Albania
Department of Pneumology Diseases, University Hospital of Lung Diseases "Shefqet Ndroqi", Tirana, Albania
Department of Statistics, University Hospital Center "Mother Theresa", Tirana, Albania
Department of Radiology, University Hospital Center "Mother Theresa", Tirana, Albania
Department of Immunology, University Hospital Center "Mother Theresa", Tirana, Albania
Department of Cardiology, University Hospital Center "Mother Theresa", Tirana, Albania
Department of Infectious Disease, University Hospital Center "Mother Theresa", Tirana, Albania

Abstract

Introduction: Systemic lupus erythematosus (SLE) is a complex sys-temic autoimmune disease, with numerous immu-nologic and clinical manifestations. 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.

Objectives: Purpose of our study was the identification of pulmonary manifestations in patients with systemic lupus erythematosus, their assessment in relation to immunological alterations, their relation to gender and assessing the sensitivity of the examinations that are used to detect lung injury.

Patients and Methods: This is a cohort prospective study that analyzed 60 patients with systemic lupus erythematosus. Patients were examined by laboratory tests such as: anti-nuclear antibody, anti double stranded DNA antibody, anticardiolipin antibodies and D dimer. Chest x-ray, pulmonary high-resolution computed tomography, computerized tomographic pulmonary angiography, pulmonary function tests and echocardiography doppler were performed for the patients.

Results: Pleural effusion was 17 patients (28%). Interstitial lung disease was 7 patients (12%), acute lupus pneumonitis 2 patients (3%), pulmonary tromboemboli 7 patients (12%) and pulmonary arterial hypertension were 3 patients (5%). Restrictive ventilator insufficiency is 19 patients (32%).

Conclusions: Pulmonary manifestations are common in SLE and have a wide spectrum. These injuries are anatomical and functional. Immunological alterations are important factor in pulmonary injuries. Gender is a factor that influences the pulmonary injuries. High-resolution computed tomography is the most sensitive examination for the detection of pulmonary manifestations in systemic lupus erythematosus.

Key words: lupus, pulmonary, pleural effusion.

Introduction

Systemic lupus erythematosus (SLE) is a complex sys-temic autoimmune disease, with numerous immu-nologic and clinical manifestations (1). 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 (2). Clinically characterized by multisystem involvement and varied serologic abnormalities, no two patients present or have disease that evolves in exactly the same way (3). 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 (4, 5, 6). A recent autopsy study of 90 patients diagnosed with SLE, according to the American College of Rheumatology, pleuropulmonary involvement occurred in 98% of the autopsies (7). 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 (8). Purpose of our study was the identification of pulmonary involvement in patients with SLE, their assessment in relation to immunological alterations, gender and evaluation of the sensitivity of the technique for the detection of lupus lung disease.

Patients and Methods

This is a prospective cohort study that analyzed 60 patients with systemic lupus erythematosus (SLE). These patients were hospitalized in the clinic of Rheumatology, Lung diseases or followed as

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outpatients. All patients fulfilled the criteria of the American College of Rheumatology (ACR) for the diagnosis of SLE (9). These patients did not have pulmonary injury or illness which in the past or currently influences pulmonary damage and not smoking or drug-induced lupus. There was no history of any occupational exposure to inorganic or organic dusts (eg.asbestosa, silicosis, coal worker's pneumoconiosis). In this study were not pregnant women and breastfeeding mothers. In the history of disease taking, patients were examined by laboratory tests tests such as: anti-nuclear antibody (ANA), anti double stranded DNA antibody (anti-dsDNA) and anticardiolipin antibodies (ACA) IgG, IgM, D dimer. Patients were examined with chest x-ray (CXR), high resolution computed tomography (HRCT) and in patients with clinical and laboratory suspicion of pulmonary embolism was used computerized tomographic pulmonary angiography (CTPA). Chest x-ray (CXR), HRCT and CTPA findings were recorded in consultation with the radiologist. Patients were examined with chocardiography doppler for pulmonary arterial hypertension (PAH) and were referred to the cardiologist for interpretation of the related findings (10). Interstitial lung disease (ILD) diagnostic criteria for this study were defined according to American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of idiopathic interstitial pneumonias (11). Diagnostic criteria for pulmonary embolism were defined according guidelines on the diagnosis and management of acute pulmonary embolism (12). Lung function was measured with spirometry. The spirometry was performed according to the American Thoracic Society (ATS) criteria (13). To determine if immunological alterations are associated with pulmonary injury, patients are classified into two groups. The first group included patients with with positive ANA, anti-dsDNA and ACA; the second group included patients with antinuclear antibodies (ANA) negative, anti-dsDNA and ACA negative. Analysis based on sex was performed to assess the scale of pulmonary injuries.

Statistical analysis

Continuous data are expressed as the average value and standard deviation. Discrete data are presented in absolute value and in percentage. The difference between discrete variables was analyzed by Kolmogorov Smirnov and Chi square test. Data were analyzed by SPSS 19.0 program. The P value $\leq 0,05$ was considered a statistically significant.

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 53 patients (88%) and 7 patients (12%) were males. ANA positive are 54 patients (90%) patients, anti-dsDNA positive are 37 patients (62%), ACA positive are 14 patients (23%), CXR injury were 9 patients (15%), pulmonary injury in HRCT are found in 26 patients (43%) and in CTPA 7 patients (12%) with tromboemboli, pulmonary arterial abnormalities are 3 patients (5%) with echocardiography doppler (ECHO) and pulmonary function abnormalities (PFTs) are 19 patients (32%) (Table nr.1).

Table nr.1. Examination data

Variables	No. of patients	Percentage %
ANA positive	54	90,0
anti-dsDNA positive	37	62,0
ACA positive	14	23,0
CXR pulmonary manifestations	9	15,0
HRCT pulmonary manifestations	26	43,0
CTPA tromboemboli	7	12,0
ECHO pulmonary arterial abnormalities	3	5,0
PFTs abnormalities	19	32.0

Lung injury is found more in HRCT compared with CXR and pulmonary function test.

Pleural effusion were 17 patients (28%), ILD is identified in 7 patients (12%), acute lupus pneumonitis (ALP) 2 4 patients (3%), pulmonary tromboemboli 7 patients (12%) and pulmonary arterial hypertension (PAH) 3 patients (5%) (Table nr.2).

Table nr.2. Pulmonary manifestations in SLE

Variables	No. of patients	Percentage (%)
Pleural effusion	17	28,0
ILD	7	12,0
Acut lupus pneumonitis	2	3,0
Pulmonary tromboemboli	7	12,0
PAH	3	5,0

Kolmogorov Smirnov=15.42, p=0.001

Pleural effusion is significant versus others pulmonary manifestations (Kolmogorov Smirnov=15.42, p=0.001).

Pulmonary function abnormalities are 19 patients (32%) and all have restrictive ventilator insufficiency. 41 patients (68%) are normal. Patients with positive ANA, anti-dsDNA and ACA were 54 patients (100%) of whom 35 patients (65%) represent pulmonary injury (group 1), while in the

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other group (group 2) of 6 patients (100%) who do not have positive positive ANA, anti-dsDNA and ACA was only 1 patients (17%) with pulmonary injury (Table nr.3).

Table nr.3. Pulmonary manifestations by immunological alterations

Variables	Patients No (%)	Pulmonary injury No (%)
Group 1	54 (100,0)	35 (65,0)
Group 2	6 (100,0)	1 (17,0)

Hi-square test =15.6, df=1, p=0.001

Pulmonary involvement in patients with immunological alteration are significant (chi-square test =15.6, df=1, p=0.001). In 7 males (100%), 2 patients (29 %) were pulmonary injury and 5 patients (71 %) indicating normal, in 53 female (100%), 34 patients (63%) were pulmonary injury and 19 are (36 %) normal (Table nr.4). Pulmonary manifestation in female are significant (chi-square test =13,5, p=0.001).

Table nr.4. Pulmonary manifestations male / female

Variables	Patients No (%)	Pulmonary injury No (%)	Normale No (%)
Male	7 (100,0)	2 (29,0)	5 (71,0)
Female	53 (100.0)	34 (63,0)	19 (36,0)
Total	60 (100,0)	36 (100,0)	24 (100,0)

chi-square test =13,5, p=0.001

Discussion

Pleuropulmonary manifestations in this study were found in 60% 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 (14). Pleural effusion, ILD, acute lupus pneumonitis, pulmonary hypertension and pulmonary trombosis are injurys that are found in these patients predominantly pleural efussion. This injury is found in 28% 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 (1). Clinically apparent effusions have been reported in up to 50% of patients and pathological involvement at autopsy in up to 93% of patients (15). Between 30% and 50% of patients with SLE will develop symptomatic pleural inflammation during the course of their disease (16). Chronic diffuse ILD is reported in a variable number of patients with SLE. ILD in this study is found in 12% patients. Diffuse ILD or chronic pneumonitis in SLE occurs in 3 to 8% of patients (8). Using only imaging criteria, the frequency is higher, between 6 and 24% on the chest radiograph and can reach 70% on CT scans (17, 18). The onset of ILD is often insidious, but it can also occur after an episode of acute pneumonitis (8). Acute lupus pneumonitis (ALP) is an uncommon manifestation of SLE, occurring in 1-4% of patients (19). Acute lupus pneumonitis has been very widely described, but in reality its frequency does not exceed 4% of cohorts (14, 19). Other autors found acute lupus pneumonitis, which occurs in up to 12% of patients or 0-14 % (6, 20). In our study, lupus pneumonitis was found in 3% patients. Pulmonary vascular involvement in lupus is also observed in our study such as pulmonary tromboemboli and pulmonary hypertension. PH in patients with SLE and antiphospholipid antibodies has been reported and described in different frequencies. The prevalence of PH in SLE is estimated to be between 0,5-43% or 2,8 -14% in others studies (21,22,23). This PH 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 (24, 25). In our study were found PAH in 5 % patients and PAH is primary. Pulmonary thromboembolism occurs in up to 25% of patients with SLE and it is an important cause of death (26, 27). In other study is foud in 7,8% (7). The presence of antiphospholipid antibodies in serum increases the probability of a thromboembolic event to 35%–42% (28). Anticardiopin antibodies of the IgG or the IgM isotype are found in 24 and 13% of the patients with SLE, and are associated with an increased prevalence of thrombosis (30% with IgG, 31% with IgM, vs 9% without), (29). In this study were found pulmonary trombomboli in 12 % patients. PFT abnormalities in patients with SLE are common and PFTs typically reveal a restrictive lung physiology (30, 31). Pulmonary function tests were abnormal in about 50% of the patients with nonspecific interstitial pneumonia (NSIP) in SLE is not well defined (32). Pulmonary function abnormalities were reported in 41% patients in other study (16). In this study PFT abnormalities are found in 32% patients with restrictive ventilator insufficiency. Pulmonary function test demonstrates restrictive ventilatory defect in all patients, although the severity

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of impairment varies and restrictive defect occurs due to ILD and pleuritis (33,19). A study identified 38% patients with CT abnormalities who had normal X rays (34). Pulmonary manifestations in HRCT in our study were 43% which is lower than the 70% and 72% reported in others stydies (17, 35). We found the HRCT is sensitive comparison with CXR and pulmonary function test. According to this study in patients with ANA positive, anti DNA positive, ACA positive pulmonary injury occurred frequently in 65% patients and we found correlation. Tissue damage and dysfunction are mediated by autoantibodies and immune complex formation (4). 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 (36). 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 (36). In our study pulmonary involvement are found in 29% in male and 63% in female. However, lung involvement in SLE can be seen more commonly in males (37).

Conclusion

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. HRCT is the most sensitive examination for the detection of pulmonary manifestations in SLE

References

1. **Capobianco J, Grimberg A, Thompson BM, et al.** Thoracic Manifestations of Collagen Vascular Diseases. RadioGraphics 2012; 32:33-50.
2. **Ferreiro L, Alvarez-Dobano JM, Valdes L.** Systemic Diseases and the Pleura. Arch Broncone-umol 2011;47(7):361-70
3. **Swigris JJ, Fischer A, Gilles J, et al.** Pulmonary and Thrombotic Manifestations of Systemic Lupus Erythematosus. Chest 2008;133:271-80
4. **Paran D, Fireman E, Elkayam O.** Pulmonary disease in systemic lupus erythematosus and the antiphospholpid syndrome. Autoimmunity Reviews 2004;3:70-5.
5. **Keane MP, Lynch JP III.** Pleuropulmonary manifestations of systemic lupus erythematosus, Tho-rax 2000; 55(2):159-66.
6. **Kim JS, Lee KS, Koh EM, et al.** Thoracic involvement of systemic lupus erythematosus: clinical, pathologic, and radiologic findings. J Comput Assist Tomogr 2000;24(1):9-18.
7. **Quadrelli SA, Alvarez C, Arce SC, et al.** Pulmonary involvement of systemic lupus erythematosus: analysis of 90 necropsies. Lupus 2009; 18:1053-60.
8. **Pego-Reigosa JM, Medeiros DA, Isenberg DA: Respiratory manifestations of systemic lupus erythematosus: old and new concepts.** *Best Pract Res Clin Rheumatol* 2009; **23**:469-80.
9. **Hochberg MC.** Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum1997; 40:1725.
10. **McLaughlin VV, Archer SL, Badesch DB, et al.** ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc, and the Pulmonary Hypertension Association. JAm Coll Cardiol 2009;53: 1573-619.
11. **Travis WD, King TE Jr, Bateman ED, et al.** American Thoracic Society/European Respiratory Society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 2002; 165:277-304.
12. **Torbicki A, Perrier A, Konstantinides S, et al.** Guidelines on the diagnosis and management of acute pulmonary embolism: The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). European Heart Journal 2008; 29:2276-315
13. **Miller MR, Hankinson J, Brusasco V, et al.** Standardisation of spirometry. Eur Respir J 2005;26:319–38.

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Number 3, Volume 44, 2013

14. **Kim EA, Lee KS, Johkoh T, et al.** Interstitial Lung Diseases Associated with Collagen Vascular Diseases: Radiologic and Histopathologic Findings. *RadioGraphics 2002;* 22:151-65.
15. **Crestani B.** The respiratory system in connective tissue disorders. Allergy 2005:60:715-34
16. Kamen DL, Strange C. Pulmonary manifestations of systemic lupus erythematosus.Clin Chest Med. 2010; 31:479–88.
16. **Fenlon HM, Doran M, Sant SM, et al**High-resolution chest CT in systemic lupus erythematosus AJR Am J Roentgenol 1996; 166:301-7.
17. **Gaude GS, Mahishale V, Srivastva A.** Pulmonary Manifestations in Connective Tissue Disorders: Chest Dis Allied Sci 2009; 51:145-51.
18. **Orens JB, Martinez FJ, Lynch JP III,** Pleuropulmonary manifestations of systemic lupus erythematosus. Rheum Dis Clin North Am 1994;20(1):159–93
19. **Cheema GS, Quismorio Jr FP.** Interstitial lung disease in systemic lupus erythematosus. Curr Opin Pulm Med 2000; 6:424-9.
20. **Johnson SR, Gladman DD, Urowitz MB, et al.** Pulmonary hypertension in systemic lupus. Lupus 2004; 13:506-9.
21. **Humbert M, Sitbon O, Chaouat A, et al**Pulmonary arterial hypertension in France: results from a national register. Am J Respir Crit Care Med 2006; 173:1023-30.
22. **Pan TL, Thumboo J, Boey ML**Primary and secondary pulmonary hypertension in systemic lupus erythematosus. Lupus 2000; 9:338-42.
23. **Carmier D, Marchand-Adam S, Diot P, et al.** Respiratory involvement in systemic lupus erythematosus. Revue des Maladies Respiratoires 2010; Volume 27, numéro 8 pages e66-e78.
24. Rockall AG, Rickards D, Shaw PJ. Imaging of the pulmonary manifestations of systemic disease. Postgrad Med J 2001; 77:621-38.
25. **Gladman DD, Urowitz MB.** Venous syndromes and pulmonary embolism in systemic lupus erythematosus. Ann Rheum Dis 1980; 39:340-3.
26. **Pines A, Kaplinsky N, Olchovsky D, et al.** Pleuropulmonary manifestations of systemic lupus erythematosus: clinical features of its subgroups. Prognostic and therapeutic implications. Chest 1985; 88:129-35.
27. **Love PE, Santoro SA.** Antiphospholipid antibodies: anticardiolipin and the lupus anticoagulant in sys-temic lupus erythematosus (SLE) and in non-SLE disorders: prevalence and clinical significance. Ann Intern Med 1990;112(9):682-98.
28. **Cervera R, Khamashta MA, Font J, et al.** Systemic lupus erythematosus: clinical and immunologic patterns of disease expression in a cohort of 1,000 patients. The European Working Party on Systemic Lupus Erythematosus. Medicine (Baltimore) 1993; 72:113-24.
29. **Nakano M, Hasegawa H, Takada T, et al.** Pulmonary diffusion capacity in patients with systemic lupus erythematosus. Respirology 2002; 7:45-49.
30. **Ramirez MP, Todd DJ.** Pulmonary Manifestations of Systemic Lupus Erythematosus. US Respiratory Disease 2011;7(1):43-8.
31. **Tansey D, Wells AU, Colby TV, et al.**Variations in histological patterns of interstitial pneumonia between connective tissue disorders and their relationship to prognosis. Histopathology 2004;44:585-96.
32. **Murin S, Wiedemann HP, Mathay RA.** Pulmonary manifestations of systemic lupus erythematosus. Clin Chest Med 1998; 19:645-65.
33. **Bankier AA, Kiener HP, Wiesmayr MN, et al.** Discrete lung involvement in systemic lupus erythematosus: CT assessment. Radiology 1995; 196:835-40.
34. **Sant SM, Doran M, Fenlon HM, et al.** Pleuropulmonary abnormalities in patients with systemic lupus erythematosus: assessment with high resolution computed tomography, chest radiography and pulmonary function tests. Clin Exp Rheumatol 1997; 15:507-13.
35. **Cojocaru M, Cojocaru IM, Silosi I, et al.** Pulmonary Manifestations of Systemic Autoimmune Diseases. Maedica (Buchar) 2011;6(3):224-9.
36. **Kamen DL, Strange C.** Pulmonary Manifestations of Systemic Lupus Erythematosus. Clin Chest Med 2010;31:479-88.