Pleuropulmonary manifestations of systemic autoimmune diseases – an 84-case series analysis

Ruža Stević1,2, Ljudmila Nagorni-Obradović2,3, Dragica Pešut2,3, Vesna Škodrić-Trifunović2,3, Nikola Ćolić1, Dragana Jovanović2,3

1Clinical Center of Serbia, Center of radiology and MRI, Belgrade, Serbia;
2University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
3Clinical Centre of Serbia, Clinic for Pulmonology, Belgrade, Serbia

SUMMARY

Introduction

The systemic autoimmune diseases (SAD) can cause a variety of pulmonary and pleural abnormalities. The aim of this paper is to review clinical and radiological characteristics of a series of patients with a systemic autoimmune disease hospitalized at a tertiary level facility.

Methods

In this retrospective study, we reviewed the clinical and imaging findings in patients diagnosed with SAD at the Teaching Hospital of Pulmonology during a nine-year period.

Results

An 84-patient group (mean age of 53.8 years) consisted of 64 women and 20 men. Fifty-eight out of 84 patients suffered from collagen vascular disease (CVD) and 26/84 had systemic vasculitis. Fatigue was the dominant symptom (75.8% in CVD, and 69.2% in vasculitis). Cough, hemoptysis, and fever were more frequent in patients with vasculitis. Fibrosis was the most common radiological manifestation of CVD (26/58), followed by pleural effusion (18/58) and consolidation (10/58). Irregular opacities were dominant radiologic finding in vasculitis (10/26), followed by nodules (8/26). Histological confirmation of systemic autoimmune disease was obtained in 28.6% patients, in 58/84 patients the diagnosis was based on a positive serologic test and clinico-radiological manifestations, in two cases on clinical and radiological features according to defined criteria.

Conclusion

Pleuropulmonary manifestations of SAD are usually expressed in the sixth decade of life, predominantly in women. Clinical findings and positive serologic tests suggest diagnosis of SAD. Fibrosis is the most common radiologic pattern found in almost one half of the patients with CVD and irregular opacities are the most common findings in vasculitis.

Keywords: autoimmune diseases; vasculitis; pleura; pulmonary; radiology

INTRODUCTION

Systemic autoimmune diseases (SAD) include a heterogeneous group of immunologic disorders whose common characteristic is the presence of an idiopathic systemic autoimmune process. These disorders include collagen vascular diseases (CVD) and the systemic vasculitis. The characteristic thoracic manifestations of the diseases are influenced by the pathophysiologic characteristics of the underlying process. The pleuropulmonary manifestations of systemic diseases are broad and vary according to the specific disease type. Several anatomic locations of the respiratory tract may be involved, including lung parenchyma, airways, vessels, pleura, and respiratory muscles [1, 2]. In some patients, pulmonary involvement belongs to prognostic factors related to mortality. The major causes of morbidity and mortality in CTD are interstitial lung diseases (ILD) and pulmonary arterial hypertension [3, 4]. Although pulmonary complications generally occur in patients with a well-established disease, lung involvement can be the first manifestation of an autoimmune disorder. Patients with CVD are at a higher risk of various malignancies, and the most frequent are breast and lung cancer, the latter most commonly detected at an advanced stage [1, 5]. Therefore, both the general practitioner and the specialist should have broad knowledge of the SAD and their complications because identification of these manifestations may initiate earlier treatment and, possibly, better disease outcome. Diagnosis of the SAD solely on a clinical basis is difficult due to mainly nonspecific presentation. Apart from that, the diagnosis is based on imaging, histopathology, biology, and autoimmune serology [2]. We aimed to analyze a group of patients with SAD in terms of their clinical, immunologic, histologic, and radiological features.

METHODS

Subjects

This retrospective study was performed on 84 patients discharged from the Teaching Hospital of Pulmonology, with diagnoses of pleuropulmonary manifestations of systemic diseases in a nine-year period. The medical files were carefully reviewed for clinical, radiological, immunological, and histological features. Clinical examination included the data of general...
and respiratory physical examination. The radiological examination included plain chest X-ray and high-resolution computed tomography (HRCT) of the thorax. Pulmonary function tests included spirometry: forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), FEV1/FVC ratio, and peak expiratory flow (PEF) [6]. Patients with hemoptysis or severe clinical imaging were not examined spirometrically, but rather pulse oximetry or arterial blood gas analysis were performed. The following investigations were also performed: complete blood count (CBC), routine urine analysis, serum levels of rheumatoid factor (latex agglutination test), antinuclear antibody (ANA) (immunoassay method), c-ANCA (antineutrophil cytoplasmic antibodies) and p-ANCA (indirect fluorescence antibody and ELISA method), C-reactive protein assay (latex agglutination test), and biopsies of different organs in 24 patients. The diagnosis was based on the evaluation of clinical and radiological manifestations, serological tests, and histological analyses of the involved organs.

The study was done in accordance with the institutional Committee of Ethics.

Statistical analysis

Statistical analysis was performed using the statistical program R–version 3.1.1 (2014-07-10) “Sock it to Me, Copyright (C) 2014; the R Foundation for Statistical Computing; Platform: x86_64-w64-mingw32/x64 (64-bit); (22.10.2014). Descriptive statistics were used to summarize baseline patients’ demographic and clinical characteristics. The results were expressed as mean ± standard deviation for continuous variables and as percentages for categorical variables. Testing of normality of the data with normal distribution was performed using graphics: normal Q-Q plot and histogram, and Kolmogorov–Smirnov and Shapiro–Wilks test. Continuous variables were compared by the Wilcoxon or the Kruskal–Wallis test. Categorical variables were comparing using the χ2 test and the Fisher’s exact test. A p-value < 0.05 was considered statistically significant. In the case of multiple testing on the same data set, Bonferroni correction was used (α = 0.05/6 = 0.0083).

RESULTS

The study group of 84 patients with SAD included 76.2% women and 23.8% men. The patients’ age ranged from 19 to 83 years (mean being 53.8 ± 13.8 years) with predominance of those between 41 and 70 years. Patients with systemic vasculitis were significantly younger than those with CVD (p < 0.017).

Clinical characteristics

We reviewed 58 patients with CVD and 26 with systemic vasculitis. Frequency distribution of the diseases is shown in Figure 1. Among patients with CVD, female patients prevailed (49/58). There was no significant sex frequency difference in the group of patients with primary systemic vasculitis. The average age at the onset of disease was 43.7 ± 14.05 years in patients with CVD, and 48.3 ± 11.9 years in patients with vasculitis (p = 0.128). Eighty-one (96.4%) patients had two or more symptoms and only three patients with CVD had only one symptom. Overall, the dominant symptom was fatigue. Cough, hemoptysis, and fever were more frequent in patients with vasculitis (Table 1). The duration of symptoms varied from a few weeks to 35 years. Thirty-two patients (38.1%) were non-smokers, 13 (15.4%) were smokers, and 7 (8.3%) ex-smokers. Thirty-four (40.5%) patients were exposed to environmental tobacco smoke. Lung function tests were done in 47/84 patients. Disorder of pulmonary function was found in 41 (87.2%) patients: in 29 with CVD and in 12 with vasculitis. The most common pulmonary function disorder tested with spirometry was restriction in 18 (38.3%) patients, followed by mixed pulmonary ventilation disorder in 13 (27.7%) and obstruction in 10 (21.3%) patients. Arterial blood gas analysis performed in 37 (44%) patients showed that 27 (71.0%) of the investigated patients experienced combined pO2 and pCO2 disorders and six (16.2%) had hypoxemia. The analysis of ABC revealed anemia in six patients with CVD and in 10 with vasculitis. Raised erythrocyte sedimentation rate was found in 46 patients with CVD and in

| Symptoms       | CVD      | Vasculitis | Total | P     |
|----------------|----------|------------|-------|-------|
|                | n (%)    | n (%)      | n (%) |       |
| Cough          | 37 (63.8)| 24 (92.3)  | 61 (72.6)| 0.0285|
| Hemoptysis     | 7 (12.1) | 17 (65.4)  | 24 (28.6)| 0.001 |
| Chest pain     | 23 (39.6)| 3 (11.5)   | 26 (30.9)| 0.614 |
| Dyspnea        | 37 (63.8)| 13 (50)    | 50 (59.5)| 0.077 |
| Fever          | 24 (41.4)| 12 (46.2)  | 36 (42.8)| 0.020 |
| Fatigue        | 44 (75.8)| 18 (69.2)  | 62 (73.8)| 0.325 |
| Arthralgia     | 22 (37.9)| 7 (21.9)   | 29 (34.5)| 0.0123|
| Loss of weight | 16 (27.6)| 2 (7.7)    | 18 (21.4)| 0.551 |

CVD – collagen vascular diseases
20 patients with vasculitis. Elevated levels of serum urea and creatinine were detected in 22 patients. All patients with CVD had positive serologic tests and all but two patients with vasculitis had positive ANCA values. We found concomitant manifestations in 38 patients with CVD: cardiovascular in 14, hematological in nine, kidney failure in six, three patients had pulmonary thromboembolism, and the other three had hypothyreosis. Three of them suffered from carcinoma (endometrium, urinary bladder, and stomach, respectively). Sixteen patients with vasculitis had a generalized form of the disease, including renal failure, and in 10 patients with limited form GPA, upper respiratory tract was also involved.

**Radiological characteristics**

Lung fibrosis was the most common manifestation of CVD in our patients, followed by consolidation and pleural effusion (Table 2). A significant correlation was found between the duration of the symptoms and fibrosis (p < 0.000). Fibrosis was diagnosed on HRCT examination in nearly one half of patients with CVD and in one patient with microscopic polyangiitis (Figure 2, Table 3). Fibrosis was predominant in women. Only three out of 27 patients were males with rheumatoid arthritis (RA). Lung consolidations were observed in 1/5 of patients with CVD, most frequently in systemic lupus erythematosus (SLE). All the patients had unilateral consolidation, but one SLE patient with acute bilateral pneumonitis. Pleural effusion frequency distribution is presented in Table 2. In seven cases, pleural effusion appeared prior to the diagnosis of a systemic disease, and in other cases 1–30 years after reaching the diagnosis (Figure 3). There was no correlation between the appearance of pleural effusion and the duration of the systemic disease. Irregular consolidations were the dominant radiologic finding in GPA (Figure 4), followed by nodules. Cavitations were detected in five of eight cases.
with nodules (Figure 5) and in three cases with consolidations. The diagnosis was based on a positive serologic test and on clinico-radiological manifestations in 58 patients, and in two cases with ankylosing spondylitis, on clinical and radiological features according to the Roma criteria. Histological verification was achieved in 24 (28.6%) patients from biopsy specimens of the affected organs (lung in 16, kidneys in five, oral mucosa in two, and larynx in one case).

DISCUSSION

Clinical features

In the presented series of our patients with SAD, CVD were more frequent than systemic vasculitis, which corresponds to the literature data. Female patients prevailed in the group with CVD [7]. Contrary to some literature data, the age at onset of CVD and vasculitis were similar in our study, being mostly expressed in the fifth and six decades of life [8]. The dominant symptom was fatigue, slightly more frequent in patients with CVD. Some other studies reported similar frequency of fatigue in SAD that ranged from 70% in Sjögren’s syndrome to 80% in systemic sclerosis and RA. The cause of fatigue in SAD is still unclear and some studies explain it by peripheral immune activation and systemic inflammation either directly or indirectly by mitochondrial damage induction [9, 10]. Similarly, according to some other studies, the lung function test abnormalities were found predominantly in patients with CVD [11]. Most of investigated patients had combined pO2 and pCO2 disorders and six (16.2%) had hypoxemia without the pCO2 disturbance. Considerable proportion of our patients had been exposed to tobacco smoke contents through active or passive smoking. It is evidence-based that oxidative and nitrosative stress and exacerbation of chronic inflammation can contribute to the development of autoimmune diseases [12, 13]. Usual peripheral blood laboratory tests were nonspecific and they pointed to an inflammatory syndrome. Concomitant manifestations were frequent in patients with CVD. Cardiovascular events are the major cause of premature death in these patients. Accelerated atherosclerosis is considered the primary cause of cardiovascular diseases and side effects of immunotherapy can also contribute to these diseases [2, 14]. Anemia is a very common abnormality associated with systemic diseases. Recognition of anemia in CVD is very important and correction of anemia is dependent on the correction of underlying CVD [15]. Renal involvement as a concomitant manifestation was present mostly in patients with SLE and in 16 patients with vasculitis, renal failure confirmed generalized form of the disease [16]. Three patients with CVD at the time of analysis had diagnosed carcinoma but none had lung carcinoma. Connective tissue disease represents a large group of diseases which can be associated with carcinoma of different localizations, and most frequently with breast and lung cancers [5, 14]. Risk factors for lung cancer development in connective tissue disease are still the subject of basic research. The effects of immunosuppressive therapy on cancer risk remain controversial [5].

Radiological characteristics

In patients with CVD, lung involvement was manifested dominantly with lung fibrosis followed by consolidations and pleural effusion. In concordance to literature data, all patients with systemic sclerosis, Sjögren’s syndrome, mixed connective tissue disease (MCTD), polymyositis, and about a half of the patients with RA had lung fibrosis [17, 18, 19]. Some studies showed 20–80% prevalence of pulmonary fibrosis in patients with scleroderma [3, 11, 18]. The other studies reported ILD in 20–68% of patients with RA [11, 17–20], in up to 65% patients with polymyo-
Systemic autoimmune diseases

Systemic lupus erythematosus (SLE) [26, 27], rheumatoid arthritis (RA) [19], systemic sclerosis (SSc) [17, 20], and idiopathic interstitial pneumonias (IIP) [17, 20] are the most common conditions associated with ILD. RA-ILD is characterized by diffuse, bilateral, and pleural effusion. Goodpasture syndrome in one patient manifested with alveolar opacities. Diffuse, bilateral, and low-density patterns in vasculitis corresponded to diffuse hemorrhage and capillaritis on pathologic examinations [28, 30, 31]. Enlarged sample size could examine these findings in the future.

Study limitations

Retrospective design of our study is one of the limitations which is subject to recall bias and possible non-uniformity of the collected data. In addition, we were unable to make any conclusions regarding some of the SAD due to limited sample size. The fact that our study group included SAD patients from the pulmonology referral center is subject to selection bias, which limits the value of the presented findings since the cohort is not representative of all possible autoimmune-disease patients with pleuropulmonary manifestations in the population. Despite the limitations, our study may offer a broad description of a variety of thoracic manifestations of systemic diseases.

CONCLUSION

The SAD can cause a variety of pulmonary abnormalities, predominantly expressed in women in the sixth decade of life. Identification of the pattern-associated antibodies and correlation with clinical findings are necessary for the diagnosis of CTDs. Pulmonary fibrosis is the most common radiologic pattern in CVD, and poorly specific irregular opacities dominate in vasculitis. The pleural cavity is the most affected site in RA and SLE. In order to recognize, diagnose, and manage the SAD in a timely manner, associated efforts and skills of clinicians, radiologists, and pathologists are of the utmost importance.

ACKNOWLEDGEMENT

This work was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia, contract No. 175046.

Conflict of interest: None declared.
Плеуропулмонална испољавања системских аутоимунских обољења — анализе серије од 84 случаја

Ружа Стевић1,2, Људмила Нагорни-Обрадовић2,3, Драгица Пешут2,3, Весна Шкодрић-Трифуновић2,3, Никола Чолић1, Драгана Јовановић2,3
1Клинички центар Србије, Центар за радиологију и магнетну резонанцу, Београд, Србија; 2Универзитет у Београду, Медицински факултет, Београд, Србија; 3Клинички центар Србије, Центар за радиологију и магнетну резонанцу, Београд, Србија

САЖЕТАК
Увод Системске аутоимунске болести могу узроковати разне плућне и плућне аномалности. Циљ овог рада је да се прикажу клиничке и радиолошке карактеристике серије болесника са системским аутоимунским болестима хоспитализованима у терцијарној установи. Методе У овој ретроспективној студији прегледали смо клиничке и радиолошке налазе код болесника са дијагнозом системских аутоимунских болести на Универзитетској болници за плућне болести током деветогодишњег периода. Резултати (рупа од 84 болесника (средња старост 53,8 година) састојала се од 64 жене и 20 мушкараца. Подсет осим од 84 болесника (69,04%) било је од колагене васкуларне болести (КВБ), али 26 од њих имало је системска васкулитисе. Дијагноза је заснована на позитивним серолошким тестовима и клиничко-радиолошким испољавањима, у два случаја на клиничким и радиолошким карактеристикама према дефинисаним критеријумима. Закључак Плеуропулмонална испољавања системских аутоимунских болести обично се јављају у шестој деценији, пре током дугогодишњег периода.

DOI: https://doi.org/10.2298/SARH190730061S

Srп Arh Celok Lek. 2020 Sep-Oct;148(9-10):535-540

7. Cincinelli G, Generali E, Dudam R, Ravindran V, Selmi C. Why women or why not men? Sex and autoimmune diseases. Indian J Rheumatol. 2018;13:44–50.
8. Antin-Oervski D, Swigris J. Pulmonary complications of connective tissue disease. Semin Respir Crit Care Med. 2014;35:157–8.
9. Pryce CR, Fontana A. Depression in autoimmune diseases. In: Dantzer R, Capuron L. Inflammation-associated depression: Evidence, mechanisms and implications. Cham: Springer; 2016. p. 139–54.
10. Morris G, Berk M, Walder EA, Mie M. Central pathways causing fatigue in neuro-inflammatory and autoimmune illnesses. BMC Med. 2015;13:28.
11. Ciancio N, Pavone M, Torrisi SE, Vancheri A, Sambataro A, Palmucci S, et al. Contribution of pulmonary function tests (PFTs) to the diagnosis and follow up of connective tissue diseases. Multidiscip Respir Med. 2019;14:17.
12. Gawda A, Majka G, Nowak B, Marcinkiewicz J. Air pollution, multimorbidity and the ageing lung. Eur Resp J. 2016;47(5):1535–43.
13. Pentony P, Duquenne L, Dutton K, Mankia K, Gul H, Vital E, et al. Why are there so many women with systemic lupus erythematosus? Semin Respir Crit Care Med. 2015;13:28.
14. Wang X, Lou M, Li Y, Ye W, Zhang Z, Jia X, et al. Cardiovascular involvement in connective tissue disease: The role of interstitial lung disease. PLoS ONE. 2015;10(3):e0121976.
15. Witmer CM. Hematologic manifestations of systemic disease (including iron deficiency, anemia of inflammation and DIC). Pediatr Clin North Am. 2013;60(6):1337–48.
16. Kronbichler A, Mayer G. Renal involvement in autoimmune connective tissue diseases. BMC Med. 2013;11:95.
17. Spagnolo P, Cordier JF, Cottin V. Connective tissue diseases, fibrosis and the ageing lung. Eur Resp J. 2018;70(10):1544–54.
18. Saha K, Pleura: In connective tissue diseases. J Assoc Chest Physicians. 2016;4:6–9.
19. Nasser M, Cottin V. The Respiratory system in autoimmune and inflammatory vascular diseases. Respiration. 2018;96(1):12–28.
20. Doyle TJ, D’Cruz DP. Pulmonary manifestations of systemic lupus erythematosus. Semin Respir Crit Care Med. 2019;40(2):227–34.
21. Schirmer JH, Wright MN, Vorthein R, Herrmann K, Nolle B, Both M, et al. Clinical presentation and long-term outcome of 144 patients with microscopic polyangiitis in a monocentric German cohort. Rheumatology (Oxford). 2016;55(1):71–9.
22. Schirmer JH, Wright MN, Vorthein R, Herrmann K, Nolle B, Both M, et al. Clinical presentation and long-term outcome of 144 patients with microscopic polyangiitis in a monocentric German cohort. Rheumatology (Oxford). 2016;55(1):71–9.