DOI: https://doi.org/10.2298/SARH190730061S
UDC: 616-097:616.24

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

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

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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

Received • Примљено: July 30, 2019
Revised • Ревизија: August 14, 2020
Accepted • Прихваћено: August 15, 2020
Online first: September 8, 2020

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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 (anti-neutrophil 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.

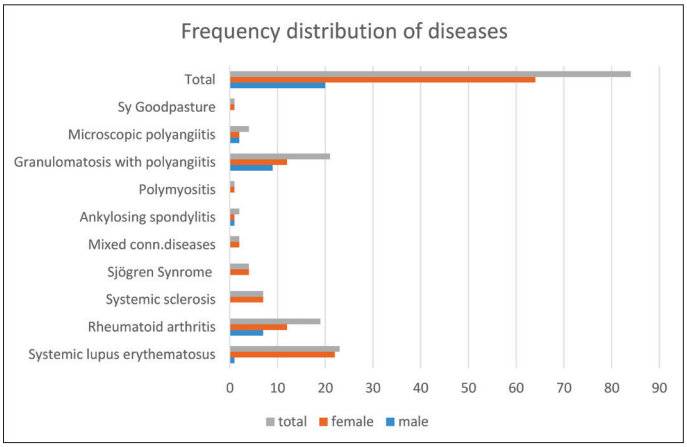

Figure 1. Frequency distribution of diseases

Table 1. Clinical presentation of the patients with systemic autoimmune diseases (n = 84)

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

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–Wilk tests. Continuous variables were compared by the Wilcoxon or the Kruskal–Wallis test. Categorical variables were compared using the χ^2 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 ($\alpha_1 = 0.05/6 = 0.0083$).

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. Thirty-three of these were patients with CVD. 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 (81.8%) of the investigated patients experienced combined pO_2 and pCO_2 disorders and six (16.2%) had hypoxemia. The analysis of CBC 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

Table 2. Radiologic presentation of systemic autoimmune diseases

Radiologic finding→ Disease↓	Pleural effusion	Fibrosis	Consolidation	Other	Total
Systemic lupus erythematosus	11	3	7	2 (1 bulla, 1 tracheal stenosis)	23
Rheumatoid arthritis	7	8	3	1 (adhesions)	19
Systemic sclerosis	0	7	0	0	7
Sjögren's syndrome	0	4	0	0	4
Ankylosing spondylitis	0	1	0	1 (bulla)	2
Mixed connective tissue disease	0	2	0	0	2
Polymyositis	0	1	0	0	1
Granulomatosis with polyangiitis	0	0	10	8 nodules 2 thickened bronchovascular bundles 1 ground glass opacity	21
Microscopic polyangiitis	1	1	0	1 thickened bronchovascular bundles 1ground glass opacities	4
Sy Goodpasture	0	0	0	1 alveolar opacity	1
Total	19	27	20	18	84

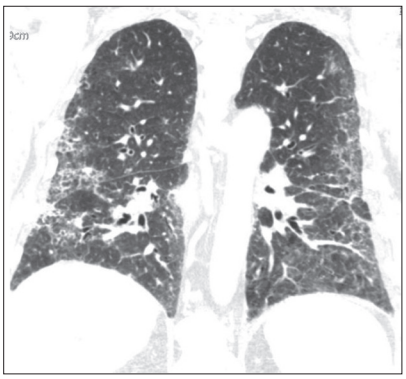

Figure 2. Coronal chest computed tomography view in lung window setting in a patient with systemic sclerosis shows thickened interstitium with ground glass opacities in peripheral parts of both lungs

Table 3. Frequency of interstitial lung diseases in systemic autoimmune diseases

Diseases	NSIP	UIP	OP	Indeterminate	LIP	Total
Systemic sclerosis	6	1	0	0	0	7
Rheumatoid arthritis	2	6	1	0	0	9
Sjögren's syndrome	3	0	0	0	1	4
Systemic lupus erythematosus	0	0	1	1	0	2
Mixed connective tissue disease	0	1	1	0	0	2
Polymyositis	1	0	0	0	0	1
Microscopic polyangiitis	0	1	0	0	0	1
Ankylosing spondylitis	0	0	0	1	0	1
Total	12	9	3	2	1	27

NSIP – nonspecific interstitial pneumonia; UIP – usual interstitial pneumonia; OP – organizing pneumonia; LIP – lymphoid interstitial pneumonia

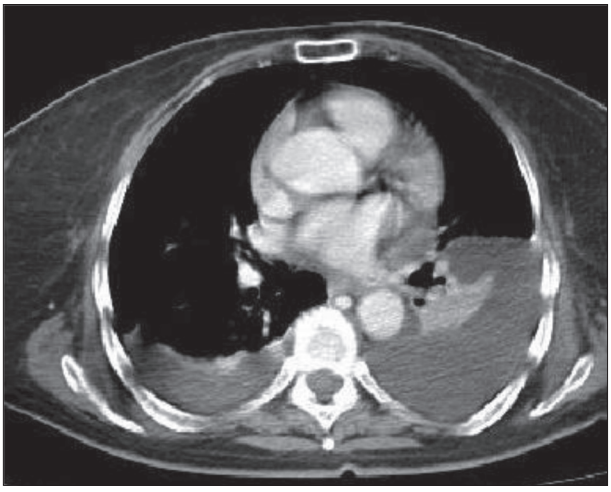

Figure 3. Axial computed tomography scan in soft tissue window shows bilateral pleural effusion, more prominent on the left side in a female patient with systemic lupus erythematosus

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

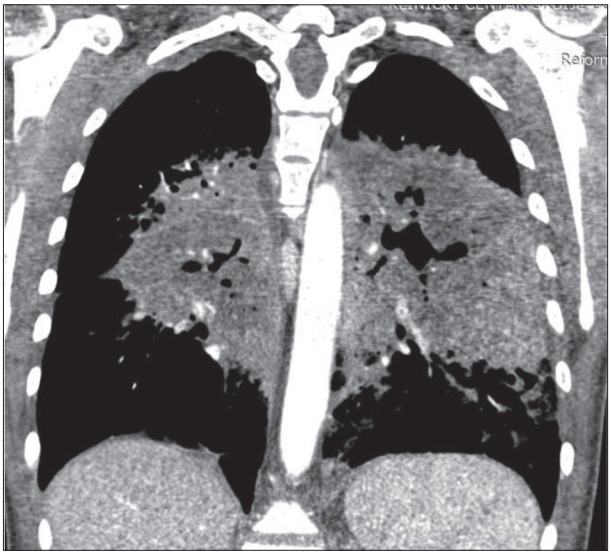

Figure 4. Coronal computed tomography view in a soft tissue window setting in a female patient with granulomatosis with polyangiitis shows irregular parenchymal consolidation with a cavitation in both lungs

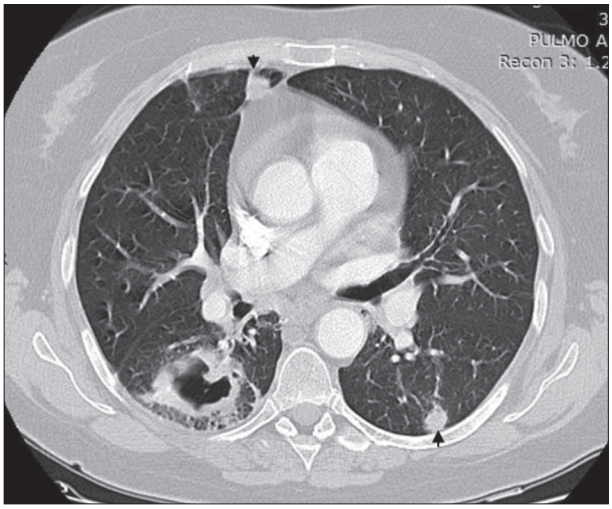

Figure 5. Axial computed tomography view in a lung window setting demonstrates a large cavitary mass with thick irregular borders in the right lower lobe, and the nodules in both lungs (arrows) in granulomatosis with polyangiitis

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 pO_2 and pCO_2 disorders and six (16.2%) had hypoxemia without the pCO_2 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-

sitis/dermatomyositis (PM/DM) [11, 21], in 21–66% % cases with MCTD [3], and in 8–38% of Sjögren's syndrome [11, 22]. Pleuropulmonary abnormalities in ankylosing spondylitis are associated with findings such as upper lobe fibrobullous disease, nonspecific interstitial changes, septal and pleural thickening [17, 23]. Although proportions of interstitial pneumonias vary, nonspecific interstitial pneumonia prevailed in our patients with scleroderma and Sjögren's syndrome. This is consistent with the findings of other studies in which reticulations and ground glass opacities were the most common HRCT abnormalities [3, 17, 18, 20]. Similarly to previously reported series, in our patients with rheumatoid arthritis, usual interstitial pneumonia (UIP) was most frequent ILD, but RA-ILD was more common in female patients, which differs from literature data [19, 20, 24]. This can be explained by differences in disease activity and sample size. ILD in CVD have better prognosis than idiopathic ILD, with the exception of RA-related ILD with UIP characteristics [17, 20]. Some studies reported three to four times higher mortality in patients with systemic sclerosis and RA who had ILD than in the general population. Five-year mortality rate is reported to be 35–39% after ILD diagnosis in patients with RA [19]. Consolidations were a less common finding in patients with CVD, being most frequent in SLE, followed by RA. Pneumonia was the most common cause of consolidation [17, 19, 20]. Pleural effusion was diagnosed most commonly in our patients with SLE and RA, with frequencies similar to previously reported results [22, 25, 26, 27]. Pleural involvement has been mentioned as the most common finding in SLE in many studies in the past, but has become far less frequent in the last two decades probably due to the early diagnosis of RA and a more aggressive treatment [19]. Imaging findings of pulmonary vasculitis are diverse and often poorly specific. The most characteristic findings were opacities of different appearance from nodular masses to ill-defined areas of consolidation, both of which cavitated. This finding is highly suggestive of GPA [28, 29]. A series of our patients with GPA showed differences in radiological features of the lung changes when compared with other reported series [29]. In the present study, areas of consolidation were slightly more frequent than nodules, but due to the small number of the patients, the result needs further evaluation on a larger sample size. The spectrum of radiological and clinical findings in our patients with microscopic polyangiitis ranged from interstitial fibrosis to ground glass opacities 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.

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Плеуропулмонална испољавања системских аутоимуних обољења – анализа серије од 84 случаја

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САЖЕТАК

Увод Системске аутоимуне болести могу узроковати разне плућне и плеуралне абнормалности.

Циљ овог рада је да се прикажу клиничке и радиолошке карактеристике серије болесника са системским аутоимуним болестима хоспитализованих у терцијарној установи.

Методе У овој ретроспективној студији прегледали смо клиничке и радиолошке налазе код болесника са дијагнозом системских аутоимуних болести на Универзитетској болници за плућне болести током деветогодишњег периода.

Резултати Група од 84 болесника (средња старост 53,8 година) састојала се од 64 жене и 20 мушкараца. Педесет осам од 84 болесника (69,04%) боловало је од колагене васкуларне болести (КВБ), а њих 26 је имало системске васкулитисе. Доминантан симптом је био замор (75,8% код КВБ и 69,2% код васкулитиса). Кашаљ, хемоптизије и повишена температура били су чешћи код болесника са васкулитисом. Фиброза је била најчешће радиолошко испољавање КВБ (26/58), затим плеурални изливи (18/58) и консолидације (10/58). Неправилне консолидације су биле доминантан радиолошки налаз код васкулитиса (10/26) и праћене су нодуларним променама (8/26). Хистолошка потврда системске аутоимуне болести је добијена код 28,6% болесника, код 58/84 болесника 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 аутоимуних болести обично се јављају у шестој деценији, претежно код жена. Клинички налаз и позитивни серолошки тестови указују на системску аутоимуну болест. Фиброза је најчешћи радиолошки налаз, који се налази код скоро половине болесника са колагеним васкуларним болестима, а неправилне консолидације су најчешћи налази у васкулитису.

Кључне речи: аутоимуне болести; васкулитис; плеура; плућа; радиологија