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Pleuropulmonary manifestations of systemic autoimmune diseases: An 84-case series analysis

Плеуропулмоналне манифестације системских аутоимуних обољења: анализа серије од 84 случаја

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Плеуропулмоналне манифестације системских аутоимуних обољења: анализа серије од 84 случаја

SUMMARY

Introduction/Objective 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 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 The 84 patients 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 a 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 positive serologic test and clinico-radiological manifestations, in two cases, on clinical and radiological features according to defined criteria.

Conclusion: Pleuropulmonary manifestations of systemic autoimmune diseases are usually expressed in the sixth decade of age, predominantly in women. Clinical findings and positive serologic tests suggest diagnosis of systemic autoimmune diseases. Fibrosis is the most common radiologic pattern found in almost a half of the patients with CVD and irregular opacities are most common findings in vasculitis.

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

САЖЕТАК

Увод/циљ Системске аутоимуне болести(САБ) могу узроковати разне плућне и плеуралне абнормалности. Циљ овог рада је да се прикажу клиничке и радиолошке карактеристике серије пацијената са системским аутоимуним болестима хоспитализованим у терцијарној установи.

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

Резултати Група од 84 пацијента (средња старост 53.8 година) се састојала од 64 жене и 20 мушкараца. Педест осам од 84 пацијента(69.04%) је боловало од колагене васкуларне болести (КВБ) а 26/84 је имало системске васкулитисе. Доминантан симптом је био замор (75.8% у КВБ и 69.2% у васкулитису). Кашаљ, хемоптизије и повишена температура били су чешћи код пацијената са васкулитисом. Фиброза је била најчешћа радиолошка манифестација КВБ (26/58) затим плеурални изливи (18/58) и консолидације (10/58). Неправилне консолидације су биле доминантан радиолошки налаз код васкулитиса (10/26) праћене нодуларним променама (8/26). Хистолошка потврда системске аутоимуне болести је добијена код 28.6% пацијената, у 58/84 болесника дијагноза је заснована на позитивним серолошким тестовима и клиничко-радиолошким манифестацијама, у два случаја, на клиничким и радиолошким карактеристикама према дефинисаним критеријумима.

Закључак Плеуропулмоналне манифестације системских аутоимуних болести обично се манифестују 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

INTRODUCTION

The 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 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 those prognostic factors related to mortality. The major causes of morbidity and mortality in CTD are interstitial lung diseases (ILD) and pulmonary arterial hypertension (PAH) [3, 4]. Although pulmonary complications generally occur in patients with well-established disease, lung involvement can be the first manifestation of an autoimmune disorder. Patients with CVD are at 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 specialist should have a broad knowledge of the SAD and their complications because identification of these manifestations may initiate earlier treatment and, possibly, better disease outcome. Diagnosis of systemic autoimmune diseases 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 systemic autoimmune diseases 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 data of general and respiratory physical examination. The radiological examination included plain

chest x-ray and HRCT of 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 have not been examined spirometrically, but rather, pulse oximetry or arterial blood gas analysis was performed. Following investigations have been also done: complete blood count (CBC), routine urine analysis, serum levels of rheumatoid factor (latex agglutination test), antinuclear antibody (ANA) (immunoassay method), c-ANCA and p-ANCA (indirect fluorescence antibody and ELISA method), C-reactive protein assay (latex agglutination test) and biopsies of different organs in 24 patients. Diagnosis was based on the evaluation of clinical and radiological manifestations, serological tests, and histological analysis of the involved organs.

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

Statistical analysis

Statistical analysis was performed using 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 was used to summarize baseline patients' demographic and clinical characteristics. Results were expressed as mean ± standard deviation for continuous variables and as percentage for categorical variables. Testing of normality of the data with normal distribution was performed using graphics: Normal Q-Q Plot and Hystogram, and tests: Kolmogorov-Smirnov and Shapiro-Wilk. Continuous variables were compared by Wilcoxon or Kruskal Wallis test. Categorical variables were compared using Chi square- test and 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 systemic autoimmune diseases included 76.2% women and 23.8% men. The patients' age ranged from 19 to 83 years (mean 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 characteristic

We reviewed 58 patients with CVD and 26 with systemic vasculitis. Frequency distribution of the diseases is shown by the 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 dominant symptom was fatigue. Cough, hemoptysis, and fever were more frequent in patients with vasculitis (Table 1). Duration of symptoms varied from few weeks to 35 years. Thirty-two patients (38.1%) were non-smokers, 13(15.4%) were smokers and seven (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%) patient: 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 investigated patients experienced combined pO_2 and pCO_2 disorders and 6(16.2%) had hypoxemia. 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 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 hypothyrosis. Three of them suffered from carcinoma (endometrium, urinary bladder, and stomach, one each). Sixteen patients with vasculitis had generalized form of the disease including renal failure, and in 10 patients with limited form granulomatosis with polyangitis (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). Significant correlation was found between duration of symptoms and fibrosis ($p < 0.000$). Fibrosis was diagnosed on HRCT examination in nearly a half of patients with CVD and in one patient with microscopic polyangiitis (Table 3). Fibrosis was predominant in women. Out of 27, only three patients were males with RA. Lung consolidations were observed in 1/5 of patients with CVD, most frequently in systemic lupus erythematosus (SLE). All 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 diagnosis of systemic disease, and in other cases one to 30 years after diagnosis (Fig. 3). There was no correlation between appearance of pleural effusion and duration of systemic disease. Irregular consolidations were dominant radiologic finding in GPA (Fig.4) followed by nodules. Cavitations were detected in five of eight cases with nodules (Fig. 5) and in three cases with

consolidations. Diagnosis was based on positive serologic test and clinico-radiological manifestations in 58 patients, and in two cases with ankylosing spondylitis, on clinical and radiological features according to 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 series of our presented patients with SAD, collagen vascular diseases were more frequent than systemic vasculitis that 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 decade [8]. Dominant symptom was fatigue, slightly more frequent in patients with collagen vascular diseases. The other studies reported similar frequency of fatigue in systemic autoimmune diseases 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, 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 pCO_2 disturbance. Considerable proportion of our patients has 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 disease [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 very common abnormality associated with systemic diseases. Recognition of anemia in CVD is very important and correction of anemia is dependent on correction of underlying CVD [15]. Renal involvement as concomitant manifestation was present mostly in patients with SLE and in 16 patients with vasculitis, renal failure confirmed generalized form of disease [16].Three patients with collagen vascular diseases at time of analysis had diagnosed carcinoma but none had lung carcinoma. Connective tissue disease represents a large group of disease, 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 polymyositis/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, UIP was most frequent ILD but RA-ILD was more common in female patients, which differ 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 exception of RA-related ILD with UIP characteristics [17, 20]. Some studies reported 3–4 times higher mortality in those patients with systemic sclerosis and RA who had ILD than in general population. Five-year mortality rate is reported to be from 35% to 39% after ILD diagnosis in patients with RA [19]. Consolidations were less common finding in patients with CVD, being most frequent in SLE, followed by RA. Pneumonia was most common cause of consolidation [17, 19, 20]. Pleural effusion was diagnosed most commonly in our patients with SLE and RA with the frequencies similar to previously reported results [22, 25, 26, 27]. Pleural involvement has been mentioned as the most common finding in SLE in the many studies in the past, but has become far less frequent in the last two decades probably due to early diagnosis of RA and more aggressive treatment [19].

Imaging findings of pulmonary vasculitis are diverse and often poorly specific. 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 difference in radiological features of the lung changes when compared with the 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 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 limit 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

In summary**,** systemic autoimmune diseases 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 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 most affected site in RA and SLE. In order to recognize, diagnose, and manage SAD in a timely manner, associated efforts and skills of clinicians, radiologists, and pathologists are of utmost importance.

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

Symptoms	CVD* N (%)	Vasculitis N (%)	Total N (%)	p value
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
Weight loss	16(27.6)	2(7.7)	18(21.4)	0.551

CVD – collagen vascular diseases

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
Granumomatosis with polyangiitis	0	0	10	8 nodules 2 thickened bronchovascular bundles 1 ground glass opacities	21
Microscopic polyangiitis	1	1	0	1 thickened bronchovascular bundles 1ground glass opacities	4
Goodpasture syndrome	0	0	0	1 alveolar opacities	1
Total	19	27	20	18	84

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

Disease	Nonspecific interstitial pneumonia	Usual interstitial pneumonia	OP	Undetermined	Lymphocytic interstitial pneumonia	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

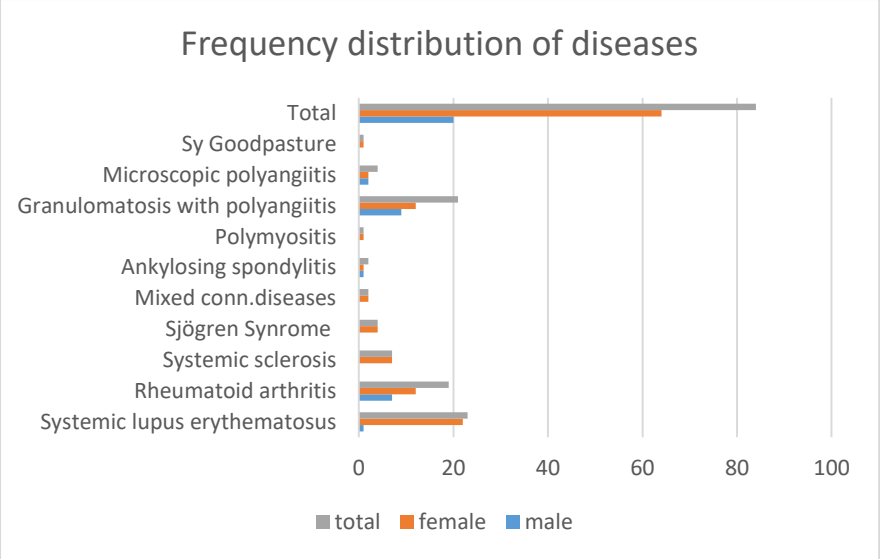

Figure 1. Frequency distribution of diseases

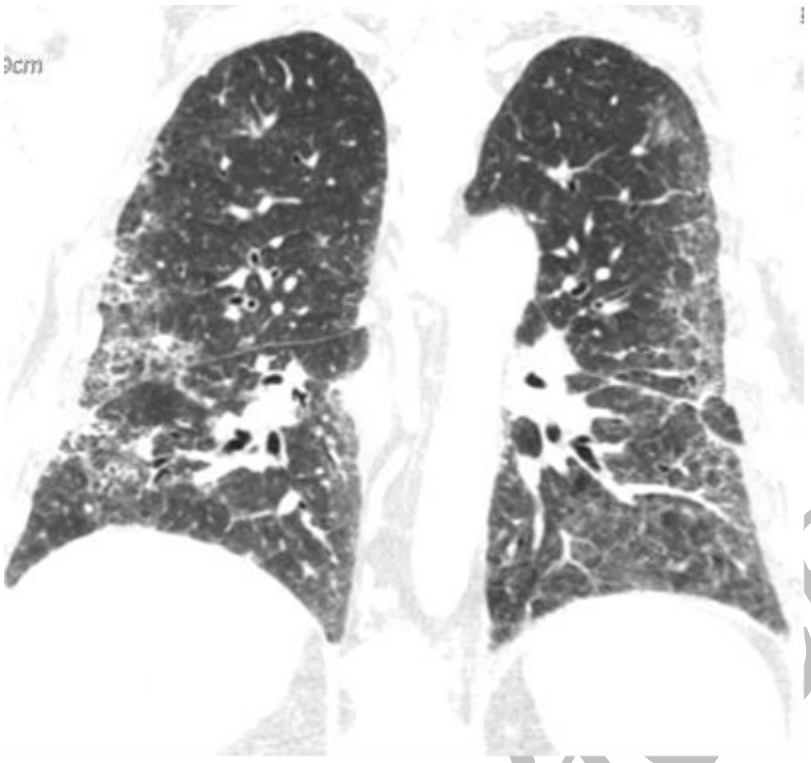

Figure 2. Coronal Chest computed tomography view in lung window setting in a patient with systemic sclerosis shows thickened interstitium with ground glass opacities in peripheral parts of both lungs

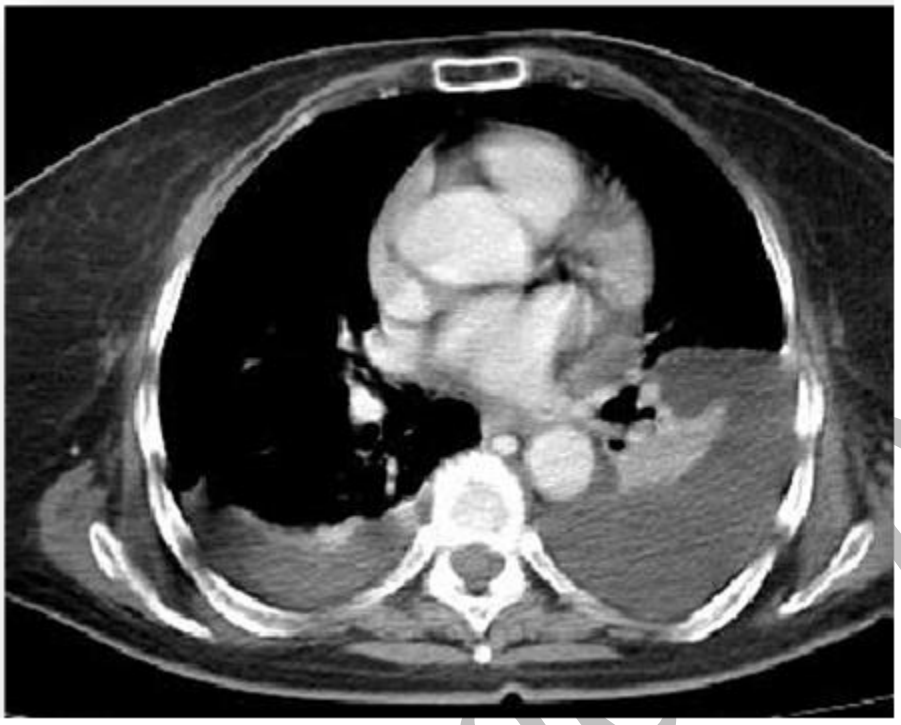

Figure 3. Axial computed tomography scan in soft tissue window shows bilateral pleural effusion, more prominent on the left side in female patient with systemic lupus erythematosus

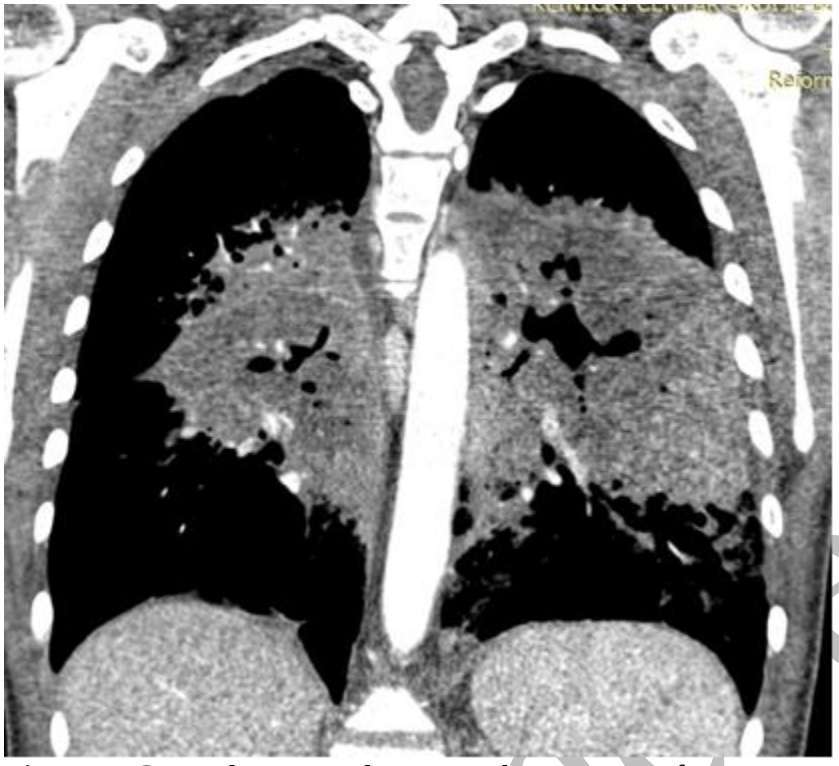

Figure 4. Coronal computed tomography view in soft tissue window setting in female patient with granulomatosis with polyangitis shows irregular parenchymal consolidation with a cavitation in the both lungs

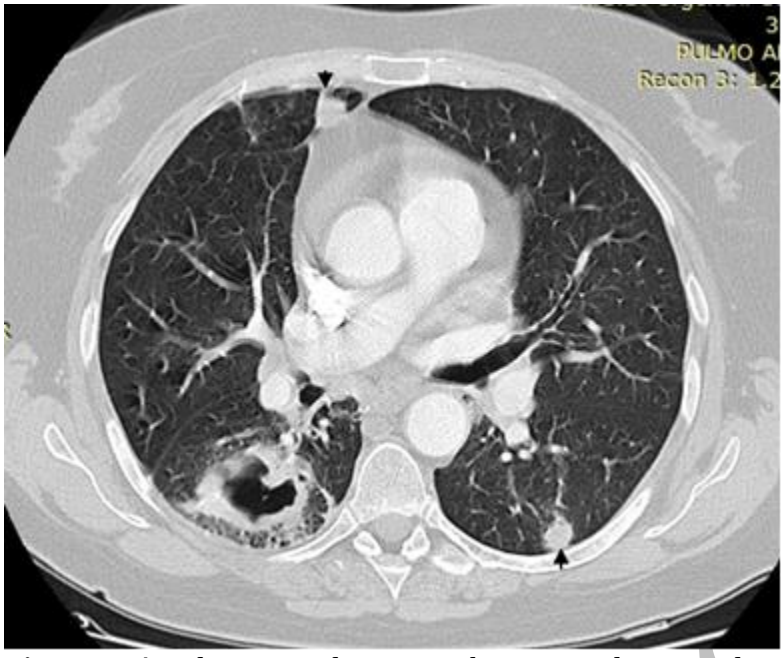

Figure 5. Axial computed tomography view in lung window setting demonstrates a large cavitary mass with thick irregular borders in the right lower lobe, and the nodules in both lungs (arrows) in granulomatosis with polyangitis

