CT Findings of Pulmonary Involvement in Antiphospholipid Syndrome

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Authors' contributions

This work was carried out in collaboration between all authors. Author AT contributed to research conception, designing the study, supervising the pulmonary function tests, analyzing the results, performing the statistical analysis and writing the manuscript. Author PS contributed to designing the study, to clinical data management, analyzing the results and writing and editing the manuscript. Author PP contributed to designing the study, evaluating and scoring the HRCT scans and editing the manuscript. Author IM contributed to research conception, to clinical data management and editing the manuscript. Author EA contributed to additional data extraction and management and editing the manuscript. Author AThomaidi contributed to performing and analyzing the echocardiographic studies and editing the manuscript. Author KR contributed to designing the study, analyzing the results and editing the manuscript. Author DB contributed to designing the study, analyzing the results and editing the manuscript. Author AO contributed to research conception, designing the study, evaluating and scoring the HRCT scans, analyzing the results, writing and editing the manuscript. She is the guarantor of the paper. All authors read and approved the final manuscript.

Research Article	

ABSTRACT

Aims: Antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterized by vascular thrombosis. Pulmonary changes regarding interstitium and

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airways have not been described in APS. Our aim was to determine the prevalence of nonthrombotic pulmonary CT manifestations in patients with APS.

Study Design: Prospective study.

Place and Duration of Study: Department of Pneumonology, First Department of Internal Medicine, Department of Cardiology, Department of Radiology Medicine, between June 2009 and May 2011.

Methodology: Ten patients who met criteria for APS (5 primary and 5 secondary to systemic lupus erythematosus) were prospectively identified. All patients underwent chest high-resolution computed tomography (HRCT) and functional assessment including spirometry and 6-minute walking distance. Patients were free of respiratory symptoms. HRCT scans were evaluated for presence of air-trapping, subpleural reticular pattern, centrilobular nodules of ground-glass opacity, cysts, emphysema, atelectasis, consolidation and pleural effusion. Extent of air-trapping was estimated based on a HRCT scoring system.

Results: All patients exhibited radiological and functional pattern compatible with small-airway disease, irrespective of smoking status. HRCT findings were negatively correlated with reduced levels of maximum midexepiratory flow (MMEF) 25/75%pred (r=-0.936, p<0.0001). Subpleural basal reticular pattern consistent with fibrosis was seen in 3 patients. Thin-walled cysts and upper-lobe hazy micronodular pattern were detected in 4 patients.

Conclusion: CT findings of patients with APS may include air-trapping, subpleural reticular pattern, centrilobular nodules of ground-glass opacity and lung cysts irrespective of smoking history and SLE coexistence. HRCT and functional assessment may be valuable tools in evaluating APS patients.

ABBREVIATIONS

(APS) Antiphospholipid syndrome; (DL$_{CO}$) Diffusion capacity of the lung for carbon monoxide; (FEV$_1$) Forced Expiratory Volume in one second; (FVC) Functional assessment included forced vital capacity; (IPF) Idiopathic pulmonary fibrosis; (MMEF $_{25/75}$ %pred) Maximum midexepiratory flow; (PFTs) Pulmonary function tests; (RV) Residual Volume; (SAD) Small airways disease; (SLE) Systemic lupus erythematosus; (SLEDAI) SLE Disease Activity Index; (sPAP) Systolic pulmonary artery pressure; (TLC) Total lung capacity; (6MWD) 6-minute walking distance.

1. INTRODUCTION

Antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterized by thrombotic events and pregnancy morbidity, in the presence of circulating antiphospholipid antibodies (aPLs) directed against negatively charged phospholipids or phospholipid-binding proteins. It can occur as a primary condition (primary APS, PAPS) or it may be secondary to other autoimmune diseases (secondary APS, SAPS), mainly systemic lupus erythematosus (SLE) [1-4].

Acute and chronic pulmonary thromboembolism in the context of APS are well recognized. In addition, there are non-thrombotic complications associated with APS including mainly pulmonary hypertension (PAH) and rarely adult respiratory distress syndrome (ARDS) and

diffuse alveolar hemorrhage (DAH) [3,5-7]. Apart from these, only two cases of fibrosing alveolitis have been reported [8,9]. However, interstitial lung disease (ILD) in systemic autoimmune diseases may reside subclinically for a long period leading to irreversible damage of the lung at the time of the onset of respiratory symptoms. In line with this, early detection of lung involvement may lead to more effective therapeutic interventions to prevent pulmonary disability in the community. In fact the incidence of pulmonary fibrosis is particularly high in the setting of several connective tissue disorders such as systemic sclerosis and rheumatoid arthritis, where respiratory dysfunction is one of the main causes of death [10]. However there has been no previous report in the literature, to the best of our knowledge about nonthrombotic pulmonary CT findings in APS. Taken together these data we sought to determine, for the first time, on a prospective basis, the CT findings of nonthrombotic pulmonary manifestations in patients with APS.

2. MATERIALS AND METHODS

2.1 Patients

This is a prospective, single-center study evaluating the nonthrombotic pleuropulmonary manifestations in otherwise asymptomatic patients with APS. We analyzed ten Caucasian APS patients, who were admitted for planned follow-up assessment of APS (primary APS) or incomplete control of SLE disease activity (secondary APS). Five patients were suffering from secondary APS associated with SLE (SLE/APS). None of the patients was admitted for respiratory reasons or new thrombotic event. APS diagnosis was confirmed according to Sapporo revised criteria [1]. Concerning the SLE/APS, SLE diagnosis was made according to 1982 American College of Rheumatology revised criteria and disease activity was assessed based on SLE Disease Activity Index (SLEDAI) [11]. Mean time from diagnosis to study enrolment was 70.6 ± 54.1 months (range 4 to 170 months). The study was approved by the Local Ethics Committee and the Institutional Scientific Review Board. All patients gave informed consent according to the Declaration of Helsinki where they agreed to the anonymous usage of their data for research purposes.

2.3 Assessment of High Resolution Computed Tomography (HRCT) Data

CT scanning was performed with the patient in the supine position with a spiral CT scanner (ProSpeed, SX Power, General Electric, Germany). Inspiratory and expiratory HRCT scans were performed from the lung apex to the base using 1 mm slice thickness at 10 mm and 20 mm intervals accordingly. The scans were scored in consensus by two observers - each with 11 and 22 years of experience in reading chest CTs - blinded to clinical and lung function information.

The following HRCT findings were evaluated according to the glossary of terms described by the Fleischner Society [12]: subpleural reticular pattern, centrilobular nodules of ground glass opacity, lung cysts, mosaic attenuation pattern, pleural effusion and pleural thickening, atelectasis, consolidation and emphysema.

1) *Subpleural reticular pattern* was evaluated as present or absent and was characterized by the presence of subpleural lines either due to the presence of thickened interlobular septae, intralobular lines or walls of honeycombing associated with or without ground-glass opacity and accompanied by traction bronchiectasis or bronchiolectasis.

2) The presence of *centrilobular micronodules of ground-glass opacity* were defined as small nodules of less than 3 mm diameter located in the centre of the secondary pulmonary lobule with hazy increased attenuation that does not obliterate the bronchial and vascular margins. This finding however was attributed to presence of respiratory bronchiolitis in current and ex-smokers.

3) *Lung cysts* were defined as round parenchymal lucencies or low-attenuating areas with a well-defined interface with normal lung surrounded usually by a thin wall. The presence and number of well-defined thin-walled lung cysts was documented.

4) Air-trapping was characterized by geographic areas of increased and decreased attenuation that were obvious or became accentuated at expiration consistent with presence of small airways disease (SAD). Air trapping in only several secondary lobules was considered a finding within normal limits and was not recorded. The total extent of SAD was estimated, based on the modification of a subjective semi-automated scoring system adapted so as to be applied for the evaluation of air-trapping according to which corresponding inspiratory and expiratory HRCT images were scored at five levels [13]: 1) origin of great vessels; 2) main carina; 3) confluence of the pulmonary veins; 4) halfway between the third and fifth section; 5) immediately above the right hemidiaphragm. The total extent of air-trapping was estimated to the nearest five percent in each of the five sections, with global extent of disease on HRCT computed as the mean of the scores.

5) Presence of *pleural effusion and pleural thickening, atelectasis, consolidation and emphysema* were also recorded.

2.4 Functional Assessment

All patients underwent functional assessment within 1 week maximum from HRCT. Pulmonary function tests, which were all carried out according to current European Respiratory Society (ERS) guidelines, included Forced Vital Capacity-FVC, Diffusing Capacity of the lung for carbon monoxide-DL_{CO}, maximum midexepiratory flow MMEF and forced expiratory volume at first second-FEV1, residual volume (RV)/total lung capacity (TLC) ratio. Reversibility of airflow obstruction was not assessed. Airflow obstruction was defined as an FEV1/FVC below the lower limit of normal (LLN) at baseline. KCO measurements were performed with a MasterLab Pro (Erich Jaeger GmbH, Wurzburg, Germany), with the single breath maneuver method; the test gas contained CO 0.25%, He 9.17% with balance air. DL_{CO} was expressed as mmol/min/kPa. A breath-holding period of 10 s (method of Jones and Meade) and discard/sample volumes of 750 mL were adopted. Smokers refrained from smoking from 24 h before the measurement; no correction for haemoglobin levels was made since this has only a very limited effect. Predicted values and the LLN were calculated by using appropriate reference values. DL_{CO} values below the LLN were considered abnormal. In addition all patients underwent provocation test with mannitol to exclude any asthmatic contribution in our functional findings. All patients underwent 6-minute walking test (6MWD), arterial blood gases for alveolar-arterial gradient, as well as estimation of systolic pulmonary artery pressure (sPAP) with transthoracic cardiac echo.

2.5 Statistical Analysis

Data are presented as median (range), No (total) unless stated otherwise. Statistical analyses were performed with nonparametric tests (Mann-Whitney U test) in order to assess statistically significant differences in functional parameters between patients with primary and secondary APS. Nonparametric (Spearman's) correlation was applied to correlate

radiological and functional data. Statistical analysis was performed with SPSS software, version 17.0. A p value of less than 0.05 was considered to be statistically significant.

3. RESULTS

3.1 Baseline Characteristics

Baseline characteristics of patients enrolled in the study are shown in Table 1.

Table 1. Baseline characteristics of the study population

Gender	
Female	6
Male	4
Mean age, years (range)	51 (27-70)
APS	
Primary	5
Secondary (SLE)	5
Smoking history, mean pack years (range)	34 (10-70)
Current smokers	2
Ex smokers	3
Never smokers	5
Previous thrombotic events	
Deep vein thrombosis	6
Pulmonary embolism	5
CNS symptoms and lesions	5
Obstetric complications	1
Treatment (n)	
Acenocoumarol	10
Aspirin	6
Methylprendisolone	5
Azathioprine	5

Data are presented as median (range), No (total) unless stated otherwise.

Five patients had PAPS and 5 had SAPS (SLE/APS). Four patients had a history of pulmonary embolism, one of them twice. None had signs of pulmonary infection or acute pulmonary embolism at the time of enrolment. The median SLEDAI for SLE/APS patients was 12 (range: 4-49). All patients were respiratory asymptomatic at the time of HRCT, meaning no patients complained for cough, dyspnea, or chest discomfort. None of the patients presented with a history of allergy or known exposure to occupational or environmental allergens. Three patients had abnormal findings on chest radiograph including subpleural reticular pattern and subsegmental consolidation.

All patients were prophylactically treated with oral anticoagulation (acenocumarol) to a target international normalized ratio (INR) 2.5-3.5. In patients with arterial disease or recurrent events combined antithrombotic treatment with low dose aspirin (100 mg/day) was used. SLE/APS patients were received additional immunosuppressive therapy consisted of methylprednisolone (4-32 mg/day) and azathioprine (100 mg/day) (Table 1).

3.2 HCRT Findings (Table 2)

Table 2. HRCT data of patients with APS

HRCT finding	Total No of patients	PAPS	APS/SLE
Air-trapping	10	5	5
Subpleural reticular pattern	3	1	2
Thin-walled cysts	4	2	2
Centrilobular micronodules of ground-glass opacity	4	2	2
Emphysema	4	3	1
Consolidation	2	1	1
Subsegmental atelectasis	1		1
Pleural thickening	1		1

Air-trapping consistent with presence of small airways disease was seen in 10 patients (100%) – 5 PAPS and 5 SAPS, 3 of whom were smokers (1 PAPS and 2 SAPS). The median score of small airway disease extent evaluated with a semi-quantitative HRCT scoring system was 43 % (range=20 - 75%) (Fig. 1).
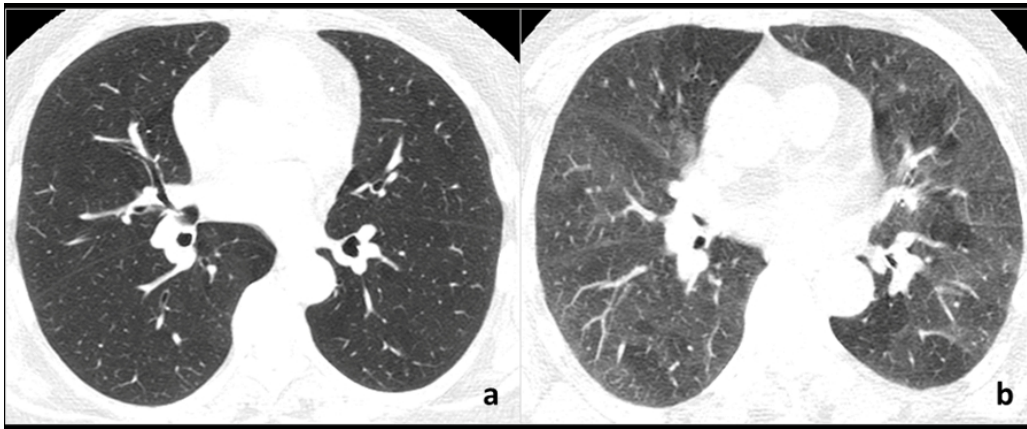

Fig. 1. Sixty-three year old female with APS. Paired inspiratory (a) and expiratory (b) HRCT images reveal air-trapping at the expiratory phase consistent with presence of small airway disease

Subpleural basal reticular pattern consistent with fibrosis was seen in 3 patients (30%), one of whom had PAPS and 2 SAPS (Fig. 2).

Fig. 2. Sixty-eight year old male with APS. HRCT image at the lower lung lobes shows subpleural reticular pattern associated with ground-glass pattern and traction bronchiolectases consistent with lung fibrosis

The reticular pattern was characterized by presence of traction bronchiolectasis associated with ground-glass opacity. No honeycombing was noted. In two of three cases subpleural sparing of several millimeters was noted. Thin-walled cysts were seen in 4 patients (40%) (2 PAPS) with maximum diameter of 1.7 cm. In two cases there was one cyst and in the other two cases two lung cysts were detected. They were all subpleurally located (in contact with the pleura) with one cyst being peripherally located (within 5 mm from the pleura) (Fig. 3).
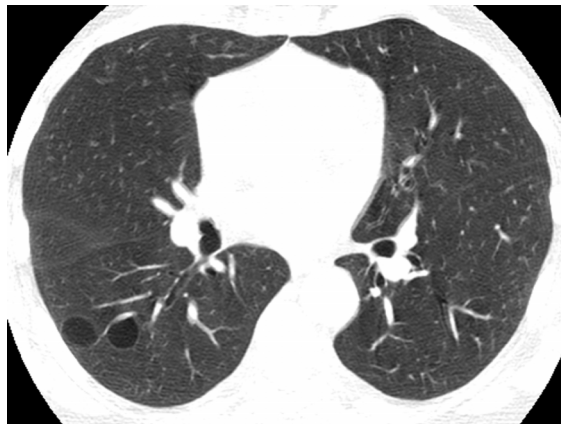

Fig. 3. Fifty-year old female with APS/SLE. HRCT image at the level of the lower lobes depicts two neighbouring thin-walled lung cysts with a subpleural location in the superior segment of the right lower lobe

Centrilobular micronodules of ground-glass opacity with upper-lobe predominance were seen in 4 patients, 3 of whom were smokers (2 current, 1 ex-smoker).

Subsegmental atelectasis and consolidation were seen in 1 and 2 patients accordingly. Mild bilateral pleural thickening was detected in 1 patient. Centrilobular emphysema was seen in 4 patients, all of whom were smokers (1 current and 3 ex-smokers) and it was attributed to the smoking habit.

3.3 Functional Assessment (Table 3)

Table 3. Functional data of patients with APS

Parameters	Data
FVC %pred	102.9 (range=75-135)
FEV_1%pred	99.3 (range=76-121)
FEV_1/FVC	80.5 (range=69-98)
MMEF $_{25/75}$ %pred	70.3 (range=36-109)
TLC %pred	104 (range=49-127)
DL_{CO} %pred	78.9 (range=40-91)
RV/TLC	105 (range=65-164)
6MWD	401 (range=240-700)
$P_{A-a}O_2$	22.5 (range=5-37)
sPAP (by echocardiography) mmHg	31.1 (range=18-48)

Data are presented as median (range), No (total) unless stated otherwise
Abbreviations: (see Abbreviations Section)

As demonstrated in Table 3, in line with radiological findings, patients with APS, either PAPS or SAPS, exhibited a functional pattern compatible with small airway disease as assessed by reduced levels of MMEF $_{25/75}$ %pred [70.3 (range=36-109)]. There were no statistical significant differences at MMEF $_{25/75}$ levels between PAPS and SAPS respectively (p=0.116) as well as between smokers (current and ex) and non-smokers (p=0.890). However small airway disease extent *(median HRCT score 43%)* was strongly negatively correlated with MMEF $_{25/75}$ %pred values in patients with APS (r=-0.936, p<0.001) (Fig. 4).
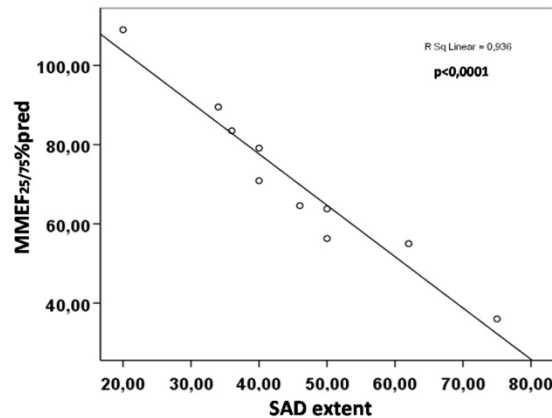

Fig. 4. An almost linear negative correlation was observed between SAD extent as assessed by thin section HRCT pattern of mosaic attenuation and air trapping and functional parameters such as MMEF $_{25/75}$ %pred values in patients with APS (r=-0.943, p<0.001)

Gas-transfer abnormality as assessed by DL_{CO} %pred was 78.9 (range=40-91). None of the patients showed any response to bronchial provocation test with mannitol compatible with asthma (data not shown). Median exercise capacity as reported by 6MWD was 401 (range=240-700), while none of the subjects showed pulmonary hypertension as estimated by transthoracic echocardiogram [median sPAP= 31.1 (range=18-48)]. Finally all patients

demonstrated normal values at alveolar – arterial gradient of oxygen tension [21.5 (range=5-37)].

4. DISCUSSION

This is the first prospective study in the literature to the best of our knowledge, investigating the CT findings of nonthrombotic pulmonary abnormalities in patients with APS compared to secondary APS in association with SLE. The findings of our study include the detection of air-trapping consistent with small airway disease in all the patients (10/10) probably independent of smoking history and SLE overlap - and the presence of subpleural basal reticular pattern consistent with fibrosis in 3 out of 10 patients as demonstrated by HRCT. The most prevalent finding of our study was the presence of air-trapping consistent with small airway disease in all our subjects. This observation was also corroborated by functional impairment and was also present in nonsmokers, meaning 5 patients - 2 with primary APS and 3 with APS/SLE - who presented with air-trapping, were lifetime non-smokers and they reported no environmental or occupational exposure. In addition none of the patients showed any response to bronchial provocation test with mannitol compatible with asthma (data not shown). Moreover, an almost linear negative correlation between small airway disease extent in HRCT and degree of functional impairment reflecting small airway dysfunction (MMEF $_{25/75}$), was also noted despite the presence of a normal RV/TLC ratio. An important problem is that, depending on age, sex and ethnic group, the intrasubject coefficient of variation for MMEF25-75% varies between 20-62% severely limiting its usefulness for clinical purposes [14]. Moreover, this variation is much less in patients with fixed obstruction and/or airway closure as was the case in our study where our subjects exhibited a mean intrasubject variation of less than 15% between three measurements on three consecutive days (data not shown). Another issue is that although RV/TLC ratio is the most reliable marker of airway closure and it has been shown that air trapping is most commonly present when RV/TLC is >135% pred [15,16] in our study RV/TLC ratio was within normal limits. However 30% of our patients had a combination of emphysema and fibrosis as indicated by the presence of subpleural reticular pattern. Therefore, the existence of two confounding factors (emphysema and fibrosis) affecting lung volumes towards two opposite directions may potentially explain this discrepancy between the decreased MMEF25/75%pred and the normal RV/TLC ratio [17]. However, this assumption may be only speculative since our study is underpowered and thus, deserves further validation. Small airway disease has been described in SLE patients -particularly in those with secondary Sjögren's syndrome [7,18,19]. Based on the close association of APS with SLE one could speculate that the high prevalence of air-trapping consistent with small airway disease may be attributed to the bronchiolitis pattern met in patients with SLE. However, air-trapping consistent with small airway disease was present in all APS/SLE as well as in all primary APS patients of our study, meaning that this pattern of small airway disease may be seen in primary APS, irrespective of SLE overlap.

In three patients of our study -all of them smokers (2 current smokers and one ex-smoker)-centrilobular micronodules of ground-glass opacity in the upper lobes were noted, a finding that was attributed to smoking related respiratory bronchiolitis [20]. In support of this finding, all these three patients exhibited also smoking-related centrilobular emphysema. However in one life-time never smoker patient with primary APS a similar pattern of centrilobular micronodules of ground-glass opacity in the upper lobes was also detected (not accompanied by emphysema) that could not be attributed to smoking history or SLE overlap.

The present study demonstrated a significantly high prevalence - 3 out of 10 - of subpleural reticular pattern compatible with pulmonary fibrosis. The HRCT pattern seen in these patients was characterized by presence of a fine reticular pattern with few traction bronchiolectases and absence of honeycombing. In one case there was relative subpleural sparing of the reticular pattern. The above mentioned findings resemble the HRCT findings of non-specific interstitial pneumonia (NSIP) pattern [21], which is actually the most common pattern of lung fibrosis in connective tissue diseases other than rheumatoid arthritis [10]. Although, structural abnormalities starkly revealed in the detailed images of HRCT were limited and unable to affect the lung functionally as assessed by normal spirometry and exercise capacity parameters, this finding reflects a potential ongoing fibrotic process that deserves further evaluation on a longitudinal basis.

There are only two cases reporting an association between APS and fibrosing alveolitis. Both patients had APS and documented alveolitis and interstitial fibrosis on pathology [5]. Although, suggestive of a potential linkage between the pathogenesis of APS and pulmonary fibrosis, both cases were published almost 20 years ago long before the classification of ILDs in 2002 [20] and the increased understanding of the HRCT appearances in the everyday clinical practice [22]. Consequently authors concluded that this rare association might simply reflect the concurrence of two entities in the same patient without a causal relationship [8,9].

A cystic pattern has not been previously reported – to the best of our knowledge – in patients with APS. However this pattern has been previously demonstrated in the context of lymphocytic interstitial pneumonia (LIP) as well as autoimmune disorders mainly Sjögren's syndrome and rarely in patients with SLE complicated by lymphocytic interstitial pneumonia [19,23]. The pathogenetic mechanism of cyst formation involves development and progression from air-trapping due to a check-valve mechanism secondary to bronchiolar stenosis from surrounding cellular infiltration [24]. Surprisingly, in our cohort, a significant number of our patients (4/10) - 2 with PAPS - revealed mainly subpleural thin-walled lung cysts, both in upper and lower lobes.

In a recently published study comparing SLE patients with or without APS, the authors report that those with APS had increased prevalence of thin-section chest CT abnormalities compared to those without APS [25]. The two most striking findings that had statistically significant difference were mosaic attenuation pattern that was attributed more to a vascular origin as well as architectural distortion and reticulation. Although the authors did not evaluate patients with primary APS as we did in our study, their findings also suggest that antiphospholipid antibodies may be determinant to the evolution of pulmonary interstitial disorders in SLE patients [25].

Recently there is growing evidence in the literature arising from experimental models of lung fibrosis supporting that tissue factor /thrombin/protease-activated receptors (PARs) pathway may mediate nonthrombotic functions such as inflammation and fibrosis [26]. One could therefore speculate that subclinical lesions seen in HRCT of patients with APS may represent areas of chronic microinflammation, fibrin accumulation and/or collagen deposition leading to tissue remodeling as a result of the hyperactivation of tissue factor /thrombin pathway [12]. Nevertheless, larger studies coupled with experimental findings are needed to prove a potential pathogenetic linkage between fibrosis and hypercoagulation.

Our study has certain limitations. First, this is an underpowered study in a small cohort of patients with primary and secondary APS. Second, there is no control group and third,

although the findings of small airway disease and interstitial fibrosis were shown in both smokers and non-smokers and none of the patients documented any environmental or occupational exposure, it is almost impossible to exclude the contribution of tobacco or environmental exposure from disease pathogenesis.

5. CONCLUSION

In conclusion, patients with either primary or secondary APS may present air-trapping, subpleural reticular pattern, lung cysts and centrilobular micronodules of ground-glass opacity independent of smoking history and SLE overlap. These structural changes may reflect minor functional abnormalities that may become severe and alter disease prognosis if left untreated, in keeping with the knowledge that lung disease is a common cause of major morbidity and mortality in connective tissue diseases [10]. Therefore, chest HRCT and PFTs could be incorporated in the clinical evaluation of APS patients. Early recognition and prompt diagnosis of SAD and ILD may lead to prompt and more effective treatment to avoid progressive pulmonary damage in APS patients. Larger studies however are needed to further support these findings.

CONSENT

All authors declare that 'written informed consent was obtained from the patients for publication of this study and accompanying images.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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