Pulmonary fibrosis and lymphocytic alveolitis associated with triple antiphospholipid antibody positivity: a diagnostic puzzle

Sirs,

To our knowledge, only two cases of fibrosing alveolitis associated with antiphospholipid antibody syndrome have been described so far (1, 2). Pulmonary fibrosis is a clinical, pathophysiological entity difficult to characterise that includes a heterogeneous group of disorders all causing the progressive destruction of lung architecture, leading to respiratory failure (3). On the other hand, primary antiphospholipid syndrome (PAPS) identifies a well defined condition at increased risk of vascular occlusion and/or pregnancy complications (4). In the spectrum of pulmonary diseases that may occur in PAPS (5), the most common are thromboembolism and pulmonary hypertension, while isolated fibrosing alveolitis is an extremely rare presentation of PAPS (1, 2).

We report the case of a 74-year-old woman, former smoker, hospitalised for worsening dyspnea, non-productive cough in the absence of fever. Her past medical history was notable for obesity (BMI 32), dyslipidemia, arterial hypertension and a triple positivity for antiphospholipid antibodies (aPL) (Fig 1-a) without history of thrombosis and pregnancy morbidity. Home therapy was calcium channel blockers, diuretics and statins.

The physical examination revealed crackles on both medium-lower lobes. Arterial blood gas analysis revealed reduced PaO2 (58 mmHg) and PaCO2 (32 mmHg). Laboratory data showed increased levels of inflammatory markers without white blood cells elevation. A pulmonary CT angiography rule out pulmonary embolism, but revealed a severe lung fibrosis, bronchiectasis and some ground-glass areas on medium and lower lobes (Fig 1-b). Due to negative CT angiogram a pulmonary scintigraphy was performed to investigate subsegmental arteries which showed two different perfusion defects consistent with areas of fibrosis, but could not allow to exclude pulmonary microembolism. Ground-glass areas on CT scan and uncertain results on perfusion scan, led to the execution of a Ga67-scintigram to better evaluate a possible alveolitis. After confirmation of an inflammatory condition (Fig 1-c), a bronchoscopy with bronchoalveolar lavage (BAL) was performed. The lavage fluid revealed a large population of T CD4+ lymphocytes (79% of total) producing high levels of TGF-beta (Fig 1-d).

Echocardiography showed normal right sections and no pulmonary hypertension. Spirometry showed a moderate/severe restrictive impairment with severe reduction of DLCO. The six minute walking test (6MWT) was interrupted after 220 meters.

Association between PAPS and interstitial lung disease is a still debated entity (5). Negative history for clear thrombotic events or pregnancy morbidity and the presence of a CD4+ T cells alveolitis led us to diagnose an interstitial lung disease with antiphospholipid antibody positivity. Furthermore high levels of TGF-beta found in BAL could be related to diffuse lung fibrosis.

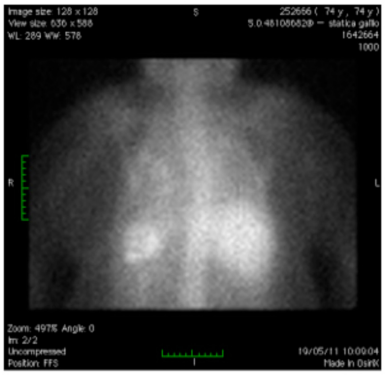
We decided to treat fibrosing alveolitis with methylprednisolone pulse therapy (125 mg/die) followed by azathioprine (75 mg/die) combined with a maintenance dose of prednisone; due to the triple aPL positivity associated with cardiovascular risk factors we started also a primary prophylaxis with low dose acetylsalicylic acid (100 mg/die). After one month of therapy the patient respiratory condition was improved, arterial blood gas analysis showed an increased PaO2 (74 mmHg) and a normal PaCO2 (36 mmHg); a new 6MWT was interrupted after 320 meters.

In conclusion, association of fibrosing alveolitis and antiphospholipid antibodies may simply reflect a stochastic coexistence of two different diseases at the same time or the antibodies may have had a role in the evolution of this particular condition.

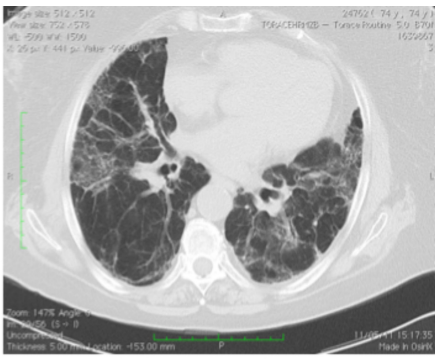
We describe a case with uncertain results, where perfusion defects are not easily ascribable to fibrosis or microthrombosis; in the light of this rare association, and recent findings of an inflammation role of antiphospholipid antibodies (6, 7), could it be worthy to start a retrospective study on fibrosing alveolitis searching for antiphospholipid antibodies.

Antbodies	First Sample	Second Sample	Normal Values
ANA	Negative	Negative	Negative
ENA Screening	Negative	Negative	Negative
Anti-dsDNA	Negative	Negative	Negative
aCL IgG	18	13	0-10 GPL-U/mL
aCL IgM	325	267	0-10 MPL-U/mL
aBeta2GPI IgG	16	11	0-10 U/mL
aBeta2GPI IgM	302	225	0-10 U/mL
LAC - SCT	2.44	2.14	< 1.16 ratio

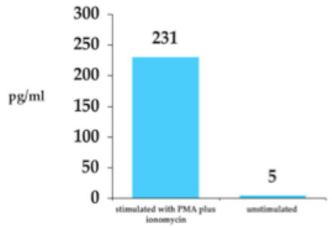
a. Antibody profile in two subsequent samples matching Sydney criteria



c. Active areas on Ga67-scintigram



b. Ground-glass areas on CT scan



d. High levels of TGF-beta produced by CD4+ cells

Table and Figures

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References

1. SAVIN H, HUBERMAN M, KOTT E *et al*.: Fibrosing alveolitis associated with primary antiphospholipid syndrome. *Br J Rheumatol* 1994;33:977-80
2. KELION AD, COCKCROFT JR, RITTER JM: Antiphospholipid syndrome in a patient with rapidly progressive fibrosing alveolitis. *Postgrad Med J* 1995; 71: 233-5
3. WYNN TA: Integrating mechanisms of pulmonary fibrosis. *J Exp Med* 2011; 208: 1339-50.
4. TRIPODI A, DE GROOT PG, PENGO V: Antiphospholipid syndrome: laboratory detection, mechanisms of action and treatment. *J Intern Med* 2011; 270: 110-22.
5. STOJANOVICH L: Pulmonary manifestation in antiphospholipid syndrome. *Autoimmun Rev* 2006; 5: 344-8.
6. AMES PRJ, ANTINOLFI A, CIAMPA A *et al*.: Primary antiphospholipid syndrome: a low grade auto-inflammatory disease? *Rheumatology* (Oxford) 2008; 47: 1832-7.
7. SATTA N, DUNOYER-GEINDRE S, REBER G *et al*.: The role of TLR2 in the inflammatory activation of mouse fibroblast by human antiphospholipid antibodies. *Blood* 2007; 109: 1507-14.