Review

The lung in the spectrum of antiphospholipid syndrome

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ABSTRACT

Patients with antiphospholipid syndrome may develop various lung manifestations. The lung complications that have been described so far are pulmonary thromboembolic disease, pulmonary hypertension, acute respiratory distress syndrome, primary thrombosis of large and small lung vessels, diffuse alveolar haemorrhage, fibrosing alveolitis and postpartum syndrome. Clinicians should be aware of these conditions as in most of these cases, timely diagnosis and treatment is needed.

Introduction

The antiphospholipid syndrome (APS) is characterised by venous and/or arterial thrombosis and/or pregnancy morbidity in the presence of antiphospholipid antibodies (aPL). Antiphospholipid antibodies are a group of antibodies including the lupus anticoagulant (LAC), anticardiolipin antibody (aCL) and anti-beta 2 glycoprotein I antibodies (anti-b2GPI) (1). Classification criteria stress that aPL should be repeatedly positive and in medium or high titer. The presence of aPL without the relevant clinical manifestations is not enough to classify a patient as APS, and it is not always a risk factor for thrombosis.

The APS is currently classified as primary APS, APS associated with other autoimmune diseases (*e.g.* SLE), and catastrophic APS (CAPS), which is characterised by widespread occlusion of small vessels, mainly affecting parenchymal organs and leading to multiple organ dysfunction.

Antiphospholipid syndrome is an hypercoagulable state and its predominant clinical features are deep venous thrombosis, stroke, pulmonary embolism, superficial thrombophlebitis, transient ischaemic attacks and obstetric manifestations.

Pulmonary manifestations in antiphospholipid syndrome

The APS has been associated with various pulmonary manifestations, many of which may occur simultaneously in the same patient (2). Pulmonary thromboembolic disease (3), pulmonary hypertension (4), acute respiratory distress syndrome (ARDS) (5) and diffuse alveolar haemorrhage are among the most common (6, 7), while fibrosing alveolitis and a postpartum syndrome are less frequently noted (8).

However, some of these associations should be taken cautiously, either because the number of patients with the reported association is small or because the association was based in the presence of aPL rather than APS (Table I). This means that the reported patients had a laboratory abnormality, but they lacked evidence of thrombotic events.

Antiphospholipid antibody syndrome *per se* does not have an effect on the pulmonary function tests. If such abnormalities are found, they should be attributed to the specific manifestation rather than the APS itself. Paran *et al*. studied pulmonary function with spirometry and single breath diffusion capacity of carbon monoxide (DLCO) in patients with SLE with or without aPL or APS. Patients with SLE without APS presented significantly reduced forced vital capacity (FVC), forced expiratory volume in one sec (FEV1), and DLCO, in comparison to patients with APS (9).

Similarly, APS does not present any specific thoracic imaging features. Gilkeson *et al*. reviewed all thoracic imaging studies in a cohort of 88 patients with aPL but not SLE. All patients had a chest x-ray with more frequent findings being subsegmental atelectasis and central pulmonary artery enlargement, each in 11% of patients, pleural effusions (5%) and scattered fo-

Table I. Pulmonary manifestations of the antiphospholipid syndrome – summary and unresolved issues.

Manifestation		Unresolved issues
Acute pulmonary thromboembolic disease	Commonest pulmonary manifestation of APS	Optimal duration and intensity of anticoagulation, therapeutic role of thrombolysis and vena cava filters
Pulmonary hypertension	APS can cause pulmonary hypertension via different mechanisms: pulmonary thromboembolism, heart involvement or pulmonary arterial hypertension	Non-thrombotic pathogenetic mechanisms, therapeutic role of pulmonary endarterectomy and pulmonary vasodilators
Acute respiratory distress syndrome	Usually occurs in the context of CAPS	Pathogenetic mechanisms and role of aPL
Pulmonary arterial thrombosis		
Pulmonary microvascular thrombosis		
Diffuse alveolar haemorrhage Fibrosing alveolitis	Rare manifestations, data from case reports only	Causal relationship with APS or aPL
Shrinking lung syndrome		
Postpartum syndrome	Rare syndrome but described only in association with APS	Discrimination from CAPS

cal opacities (4%). Other studies such as ventilation-perfusion scans, contrast-enhanced thoracic CT and thoracic MRI, were performed in patients with suspected pulmonary thromboembolism. The authors report that the rate of pulmonary thromboembolism was similar to that reported in the literature. In conclusion, the presence of aPL *per se* is not accompanied by specific imaging findings in the lung. Any abnormality found should be attributed to the specific clinical manifestations of the APS (10).

Acute pulmonary thromboembolic disease

Acute pulmonary thromboembolism is the first manifestation of APS in 9% of patients (11) and it is reported in 14–39% of patients during the course of the illness (8, 12, 13). However, in a recent prospective study Cervera *et al*. reported that only 2.1% of patients with APS presented pulmonary embolism in a 5-year period (14). Dyspnoea, tachycardia and pleuritic chest pain are the main symptoms as in any other cause of 'ordinary' emboli. Deep venous thrombosis, especially of the lower limbs, should always be suspected, as it occurs in up to 50% of APS patients (4, 12, 13).

Patients with APS and acute pulmonary embolism should be managed initially as any other patient. Unfractionated heparin, low molecular weight heparin, or thrombolysis should be used as recommended (15). It should be noted, however, that there is limited experience with thrombolysis for pulmonary embolism in patients with APS (16). The duration and the intensity of the subsequent oral anticoagulant therapy are still areas of uncertainty. Patients with aPL have an increased risk of recurrent thrombotic events (17), therefore the ACCP guidelines – and most experts – suggest 'indefinite' anticoagulation therapy following pulmonary embolism. However, there are data suggesting that the risk of stroke recurrence in patients with aPL (but not fulfilling APS criteria) is similar whether they were receiving aspiring or warfarin with target INR 1.4–2.8 (18). In addition, in patients with APS the risk of haemorrhage during anticoagulation is substantial, reaching 7.4% of patients in a recent 5-year prospective study (14). These data challenge the benefit of indefinite duration of anticoagulation with warfarin in patients with APS. The intensity of warfarin treatment is also a matter of controversy. For many years the standard of anticoagulant treatment was a target INR>3.0, based on observational studies (19). However, two randomised controlled trials failed to show that a target INR>3.0 is superior to a target INR of 2.0–3.0 in preventing recurrent thrombotic events. Nevertheless, one must interpret carefully these results, as both studies were underpowered, the number of events in both trials was low and a significant proportion of events occurred at suboptimal INR, therefore, they were not due to "warfarin failure" but rather to inadequate therapeutic monitoring (20, 21).

We should also mention that the use of inferior vena cava filters has not been systematically studied in patients with APS. Zifman *et al*. published a series of 10 patients with APS and recurrent thrombotic events, which underwent vena cava filter placement. Only one patient suffered PE and two patients died suddenly, and PE could not be excluded (22). Finally, it is noted that intravenous immunoglobulin might prevent recurrent thrombotic events, including pulmonary embolism, in patients with APS (23).

Pulmonary hypertension

Pulmonary hypertension (PH) is a progressive disease characterised by a sustained elevation of mean pulmonary artery pressure to more than 25 mmHg at rest or more than 30 mmHg during exercise, with a mean pulmonary-capillary wedge pressure and left ventricular end-diastolic pressure of less than 15 mmHg, as measured by right heart catheterisation (24). The latest scheme classifies pulmonary hypertension into 5 groups (25), depending on the underlying pathophysiology. Patients with APS and PH can be classified with group 1 (pulmonary arterial hypertension, either idiopathic or in the context of connective tissue diseases), group 2 (pulmonary hypertension due to left heart disease) or group 4 (chronic thromboembolic pulmonary hypertension – CTEPH).

The clinical manifestations of PH result, initially, from the inability to increase cardiac output during exercise

and later, from right-sided heart failure. Therefore, dyspnoea on exertion and fatigue are initial symptoms, while at more advanced cases angina, syncope, hepatic congestion and peripheral oedema are present. Despite recent improvements in treatment, the mortality associated with PH remains high. The observed 1-, 3- and 5-yr survival is 86, 69 and 61%, respectively (26).

In patients with APS, the contribution of PH to mortality is not known. A 5-year prospective study on morbidity and mortality in APS does not mention PH as a cause of death (14).

1. Epidemiological data on the prevalence of PH in patients with aPL/APS

The association of PH with aPL in three patients with SLE was first published by Asherson *et al*. (27, 28). Later, Alarcon-Segovia *et al*. reported five patients with PH and aPL in their first series of 500 patients with APS (29). The prevalence of pulmonary hypertension in cohorts of patients with APS has been estimated from 1.8% to 3.5% (30, 31). In a cohort of 1000 patients with APS, Cervera *et al*. reported PH in 2.2% (11).

2. Epidemiological data on the prevalence of aPL in patients with PH

Most of these data refer to the prevalence of aPL rather than APS. However, in patients with CTEPH the presence of aPL would classify them as APS, since they fulfil both the clinical and laboratory criteria.

The prevalence of aPL in patients with PH varies according to the type of PH (CTEPH *vs*. other types). Antiphospholipid antibodies have been detected in 10% to 63.6% of patients with CTEPH in different studies, while aPL are found less frequently in other forms of PH, with their prevalence ranging 4%–17.4% (32-35). In contrast, Farzaneh-Far *et al*. found no association between aPL and PH in patients with SLE, but most reports support the association of aPL with PH (36). Although aPL has been detected in different groups of PH, the presence of aPL is a strong risk factor for CTEPH in comparison to other forms of PH (odds ratio 4.2) (33, 35). The discrepancies among studies could be explained by the various assays used for the detection of various aPLs, and possibly by patient selection bias, as all these studies were retrospective. It seems that the larger the number of patients with PH studied, the less the prevalence of aPL reported (33, 35).

There seem to be no difference in the prevalence of each specific antiphospholipid antibody (*i.e*. LAC, aCL or anti-beta2-GPI antibodies) within each subgroup of PH patients. One exception is anti-beta2-GPI antibodies, which were detected in 36.4% of patients with CTEPH, but not in other groups of PH (33). Unfortunately, this is the only study in unselected PH patients in which anti-beta2-GPI antibodies have been measured.

3. Possible pathogenetic mechanisms

Two to 4% of patients with acute pulmonary embolism subsequently develop CTEPH (37, 38). Given the prevalence of acute pulmonary embolism- recurrent or not- in APS, this seems to be the main cause of pulmonary hypertension in such patients. In addition, in unselected patients with PH, the presence of aPL is strongly associated with the chronic thromboembolic form of PH (33).

However, there are several reports in the literature describing the development of pulmonary hypertension in APS, without evidence of thromboembolic disease (39-41). This suggests that other factors such as endothelin-1, pulmonary vascular endothelial cell dysfunction and platelet activation, may play a role in the pathogenesis of aPL-associated PH.

4. Management of PH

Review of the management of PH is beyond the scope of this paper, especially as guidelines on diagnosis and management of PH have been recently published by the European Society of Cardiology and the European Respiratory Society (42). Briefly, management of PH includes general measures such as exercise, oxygen therapy, diuretics, anticoagulation and digitalis and specific therapies which include different groups of vasodilatory drugs such as calcium channel blockers, prostanoids, endothelin receptor antagonists and phosphodiesterase type-5 inhibitors. However, the efficacy of these interventions depends to a large extend to the group of PH the patient belongs to. Most patients with PH in association with aPL are classified to group 4 PH (CTEPH) and a smaller percentage to group 1 PH (PAH). In group 4, patients lifelong anticoagulation is recommended in all cases, with a target INR 2.0–3.0, to prevent new thrombotic events. The treatment of choice in this group is pulmonary endarterectomy (PEA), which can potentially cure PH. These patients should be assessed by an expert surgeon to decide if PEA is feasible. In selected patients with CTEPH, *e.g*. inoperable patients, specific therapies may prove beneficial. In group 1, patients anticoagulation improves mortality rates (43), however, most patients need the above mentioned specific therapies.

Unfortunately, all the above recommendations are based on relatively weak evidence, as randomised controlled trials are lacking. This is true for PH in general and more so for aPL associated PH. The literature on the treatment of aPL-associated PH consists of case reports or small series of patients.

There are reports of patients with APS in which PEA has been performed with favourable outcomes in the majority of cases (44-46). Interestingly, the presence of aPL in high titers in patients undergoing PEA for CTEPH did not influence early mortality or major complications rate, but it was associated with increased risk of transient neurological impairment (47). Pulmonary arterial vasodilators such as iloprost and bosentan have also been used in isolated patients with aPL-associated PH (48-50).

Acute respiratory distress syndrome

Acute respiratory distress syndrome (ARDS) is a syndrome resulting from acute damage to the alveoli with persistent lung inflammation and increased vascular permeability (51). Acute respiratory distress syndrome is characterised by acute onset, bilateral radiographic infiltrates, a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO2/FiO2)

less than 200 mmHg, regardless of the level of positive end-expiratory pressure (PEEP), and no clinical evidence for an elevated left atrial pressure (52). It is most commonly caused by sepsis, pneumonia, trauma and/or aspiration.

ARDS is rare in patients with APS, unless they have the catastrophic variation of the latter. Until now, approximately 50 patients with ARDS in the context of APS have been reported the large majority of which, presented as CAPS (30, 53-55). Conversely, in an international registry of CAPS, 21% of patients presented ARDS (53). However, the role of aPL in the pathogenesis of CAPS-associated ARDS is not clear. Nakos *et al*. detected aPL in the bronchoalveolar lavage fluid (BALF) of a patient with APS who had developed ARDS (56). Maneta-Peyret *et al*. and Wiederman *et al*. could detect aPL in low titers in the BALF of patients with acute lung injury or ARDS without APS, but not in patients undergoing mechanical ventilation for other reasons (57, 58). Maneta-Peyret *et al*. suggested that aPL against phospholipids in the surfactant could impair its function, and plays a role in the pathogenesis of ARDS in general. These antibodies could have been generated locally or supplied from plasma due to increased permeability of the alveolar-capillary barrier (57). These suggestions, however, are not fully supported by the existing clinical data. First, although there is no established reference range for aPL in the BALF, the titers of aPL detected in the BALF were low, corresponding to normal serum levels. Second, in all but two patients in the above two studies, serum aPL levels were within normal levels. One alternative explanation for these findings is that aPL are generated in the context of the underlying disorder (*e.g* sepsis) and are possibly not pathogenic – they are an epiphenomenon rather than a cause of ARDS. Similarly, ARDS may be attributed to the condition which triggered CAPS, rather than the CAPS itself.

Unusual lung manifestations of APS

Pulmonary arterial thrombosis

Large pulmonary arterial thrombosis is a distinctly rare manifestation of APS, considering the fact that only six such patients have been described in the literature. Aggressive treatment, mainly with thromboendarterectomy, should be considered (8, 30, 44, 59).

Pulmonary microvascular thrombosis

Rarely, in patients with APS, thrombotic occlusions may affect only the small pulmonary arteries. In these patients, inflammation and alveolar capillaritis are lacking, therefore they cannot be classified as having diffuse alveolar haemorrhage. Glucocorticosteroids have been used successfully in this clinical setting (60, 61).

Diffuse alveolar haemorrhage

Diffuse alveolar haemorrhage (DAH) is characterised by bleeding in the alveolar space, which could be due to damage to arterioles, venules or alveolar capillaries. There are three histological forms, bland pulmonary haemorhage, diffuse alveolar damage and pulmonary (or alveolar) capillaritis. Microvascular thrombosis with or without capillaritis and rupture of small pulmonary vessels have been suggested as the pathogenetic mechanisms in the group of patients with DAH and systemic autoimmune diseases such as the APS (62, 63).

Although intrapulmonary bleeding is the hallmark of DAH, not all patients present with haemoptysis. As a result, the diagnosis, however, may be overlooked or its manifestations be attributed to another disease process. Except for haemoptysis, patients may present with symptoms ranging from cough, dyspnoea, and fever, to symptoms of acute reapiratory failure. Hypoxaemia and anaemia are usually present. Bronchoscopy and bronchoalveolar lavage are essential in confirming the diagnosis, by showing the presence of haemosiderin laden macrophages.

Diffuse alveolar haemorrhage is a rare manifestation of the APS. Therefor, before one can attribute DAH to APS, a variety of connective tissue disorders (SLE, polymyositis, Goodpasture syndrome etc) as well as uraemia, pulmonary embolism or infectious disease need to be excluded. Treatment of DHA in APS should start with high dose intravenous corticosteroids if the patient presents with severe respiratory distress. However, it is the clinical setting that will dictate whether cyclophosphamide, plasmapheresis or intravenous immunoglobulin will be necessary. If there is active bleeding, it might be necessary to withhold anticoagulation, and to restart treatment as soon as the pulmonary function has improved. Furthermore, long-term management with corticosteroids is needed in order to overcome the possibility of recurrence (30, 61, 64).

Fibrosing alveolitis

Until now, only two cases of fibrosing alveolitis with APS have been described (65, 66). In both cases, fibrosing alveolitis was confirmed with histopathological examination. Due to the limited number of cases, a causal relationship of these two clinical entities still remains to be proved.

Postpartum syndrome

This clinical syndrome consists of fever, pleural chest pain, pulmonary infiltrates and occasionally with renal insufficiency and cardiac conduction disturbances. It has been described during the postpartum period in women with APS (67, 68). On the basis of the multiorgan involvement, it has been suggested that postpartum syndrome could be a form of CAPS. This condition is an emergency and prompt treatment with steroids and occasionally with plasmapheresis is required.

'Shrinking lung syndrome'

'Shrinking lung syndrome' presents with insidious onset dyspnoea and pleuritic chest pain. It is characterised by small lung volume on chest film, dysfunction and elevation of the diaphragm, and a restrictive pattern on pulmonary function tests. Parenchymal involvement is absent (69, 70). The estimated prevalence of the syndrome is 0.5% in SLE patients; however, one case has been reported in pregnancy complicated by APS (71). Corticosteroids, rituximab and cyclophosphamide have been used with success in isolated patients (72).

Miscellaneous conditions

Cavitary lung lesions are a distinctly rare manifestation of primary APS.

Bertoli *et al*. reported a case of thromboembolic disease with secondary aseptic cavitary lung lesions (73). Torok *et al*., described a patient who presented with lung cavitations and was diagnosed as lupus with APS and plasma cell dyscrasia. Lung biopsy was consistent with venous type infarcts, areas of haemorrhage and capillary proliferation and simultaneous thrombosis of the small and medium size arteries. The lesions resolved three months after initiation of prednisone, methotrexate and enoxaparin (74).

Conclusion

Patients with APS may develop various pulmonary manifestations; some of them are more frequent such as pulmonary thromboembolism and pulmonary hypertension, while other are unusual such as diffuse alveolar haemorrhage and fibrosing alveolitis (Table I). In addition, it is well documented that patients with catastrophic antiphospholipid syndrome may present with ARDS. It is not clear, however, whether some of the rare lung manifestations are pathogenetically associated to aPL or APS, can be attributed to coexisting connective tissue diseases or are merely epiphenomena. Clinicians should be aware of these complications, as timely diagnosis and prompt treatment is needed. Long-term anticoagulation is needed in most, if not all, cases, while immunosuppression may be useful in selected patients. Recent advances in the knowledge of the role of endothelial cells, monocytes, platelets and complement in induction of thrombosis in APS, may allow the development of new targeted therapeutic approaches.

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