ANTIPHOSPHOLIPID SYNDROME AND THE LUNGS

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ABSTRACT

Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterised by recurrent thromboembolic events (arterial or venous) and/or morbidity in pregnancy (fetal loss, premature birth, or recurrent embryonic losses) in the presence of laboratory evidence of antiphospholipid antibodies (aPL). APS is a multisystem disorder. Several lung manifestations may develop in patients with APS including pulmonary embolism (PE)/infarction; thromboembolic and non-thromboembolic pulmonary hypertension (PH) (pulmonary arterial hypertension); pulmonary microthrombosis; acute respiratory distress syndrome associated with catastrophic APS; diffuse alveolar haemorrhage; and pulmonary capillaritis. Postpartum syndrome and cryptogenic fibrosing alveolitis (CFA) can be associated with APS. Pulmonary manifestations are relatively rare but are more likely to be life-threatening compared with other complications of APS. Particularly in the presence of aPL, pulmonary manifestations should be suspected in any systemic lupus erythematosus patient with clinical findings such as chest pain, dyspnoea, tachypnoea, and haemoptysis. Early diagnosis and treatment of pulmonary manifestations in APS are essential for improving mortality rates in patients with this condition. The purpose of this review is to assess current evidence around the diagnosis, prognosis, and management of patients with common and rare pulmonary manifestations of APS.

Keywords: Antiphospholipid syndrome (APS), pulmonary embolism (PE), pulmonary hypertension (PH), alveolar haemorrhage, antiphospholipid antibodies (aPL), systemic lupus erythematosus (SLE).

INTRODUCTION

Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterised by recurrent thromboembolic events (arterial or venous) and/or morbidity in pregnancy (fetal loss, premature birth, or recurrent embryonic losses) in the presence of laboratory evidence of antiphospholipid antibodies (aPL); including anticardiolipin antibodies (aCA), anti-beta 2 glycoprotein 1 antibodies (aβ2GP1), and lupus anticoagulant (LAC).[1,2] LAC effects the surface phospholipids thus disrupting the clotting time measured by the activated partial thromboplastin time. aCA and aβ2GP1 have roles in the control of coagulation-like complexes of phospholipids and protein or cofactors.[3] aPL are evaluated by two different methods: first a functional, activated partial thromboplastin time-based method for LAC, and second an immune assay for both aCA and aβ2GP1.[4]

aPL can be detected in the absence of thrombosis or fetal loss during infectious diseases, drug use, and even in healthy individuals. In this situation, it is clinically important to apply the diagnostic criteria.[3] The preliminary criteria, developed in 1999, and the classification criteria (Sapporo criteria) were modified in 2006.[2] When a patient fulfills the criteria they can be diagnosed as having autoimmune disease-associated APS if a condition such as systemic lupus erthematous (SLE) is present or primary APS if there is no concomitant disorder.[5] APS is a multisystem disorder. In a study including 1,000 patients with either primary or autoimmune disease-associated APS, various complications were found such as deep vein

thrombosis (DVT), thrombocytopenia, livedo reticularis, stroke, superficial thrombophlebitis, pulmonary embolism (PE), fetal loss, and transient ischaemic attack.[6] Several lung manifestations may develop in patients with APS, including PE/infarction, thromboembolic andnon thromboembolic pulmonary hypertension (PH) (pulmonary arterial hypertension), pulmonary microthrombosis, acute respiratory distress syndrome, diffuse alveolar haemorrhage (DAH), and pulmonary capillaritis.[7,8] Moreover, postpartum syndrome and cryptogenic fibrosing alveolitis (CFA) can be associated with APS.[9] Patients who develop two or more of these pulmonary manifestations synchronously can be described as having antiphospholipid lung syndrome.[7] The purpose of this study is to review the diagnosis, prognosis, and management of patients associated with common and rare pulmonary manifestations in APS.

PULMONARY EMBOLISM AND INFARCTION

The pulmonary manifestations secondary to APS may show a wide variability, but the common complications in the lung involve pulmonary thromboembolism and its associated sequelae, such as infarction and PH.[7] aPLs are associated with thrombosis; aβ2GP1 antibodies are not only a marker of thrombophilia, but moreover contribute to hypercoagulability.[10] In a study, venous thrombosis was independently associated with LAC.[11] PE may be the first manifestation of APS. Cervera et al.[12] prospectively examined the morbidity and mortality in 1,000 APS patients over a 10-year period. They found that 14.1% of patients had PE at initial diagnosis and incidence of new PE was 3.5% over the 10-year follow-up. PE-associated mortality occurred in 5.4% of the patients.[12] DVT, sometimes accompanied by PE, is the most common manifestation of APS. DVT occurs in 55% of APS patients and approximately half of these patients demonstrate PE (30%).[13,14] Furthermore, in a cohort study the PE recurrence rate in APS patients was observed to be as high as 7.5% in the first 5 years after the initial thrombotic event.[4]

The differential diagnosis of PE from pleuritis or pneumonitis can be difficult. Particularly in the presence of aPL, PE should be suspected in any SLE patients with clinical findings such as chest pain, dyspnoea, tachypnoea, and haemoptysis.[14] The first step in diagnosis of suspected PE is with clinical probability scoring, followed by D-dimer levels in blood, if appropriate, and chest radiography. Echocardiography, ventilation perfusion scintigraphy, and/or computed pulmonary angiography are essential for definitive diagnosis. Diagnosis of DVT can be made using Doppler ultrasound.[15]

PULMONARY HYPERTENSION

PH may be present as a separate entity or as a consequence of various clinical conditions such as PE in APS patients. In particular, recurrent pulmonary emboli may give rise to PH.[16] In addition, the microscopic pathogenesis of PH is characterised by vascular endothelial and smooth muscle proliferation, in situ thrombosis, development of plexogenic lesions of small pulmonary arteries, and fibrinoid vasculitis that can include all types of medium-sized arteries.[17] A recent study summarised the pathogenesis of PH in APS into three components: a) a cross-reactivity between aCA and anti-endothelial cell antibodies, b) the actions of aPL on the endothelium, and c) the plausible pathogenic role of anti-endothelial cell antibodies in PH.[8]

Transthoracic echocardiography (TTE) allows for estimates of pulmonary arterial pressure which can be confirmed by right heart catheterisation (RHC). Definitive diagnosis of PH requires an increase in mean pulmonary arterial pressure ≥25 mmHg at rest, measured by RHC.[18] It is suggested that aPL in SLE patients increase the risk of PH, a rare and life-threatening complication with poor prognosis.[8,19] In a study, the PH frequency was found to be higher in aPL positive than aPL negative SLE patients (25% and 2%, respectively).[20] Similarly to a previous study, Kamel et al.[21] found that patients with PH were most likely to have aCA positivity in comparison with those without PH. Conversely, Hübbe-Tena et al.[22] found no significant relationship between aPL and unlikely, possible, or likely groups of PH in SLE patients. The reported prevalence of PH in APS patients varies widely between studies, from 2–24%.[6,23] The discrepancies in these findings could be the result of different clinical features of patients at inclusion and/or different diagnostic methods, such as TTE and RHC, which can affect the prevalence of PH.

Five groups of disorders that cause PH have been described: pulmonary arterial hypertension (Group 1); PH due to left heart disease (Group 2); PH due to chronic lung disease and/or hypoxia

(Group 3); chronic thromboembolic PH (CTEPH) (Group 4); and PH due to unclear multifactorial mechanisms (Group 5).[24] Most PH patients associated with aPL are classified to Group 4 and a smaller percentage to Group 1.[25]

CTEPH is a pulmonary vascular disease caused by chronic obstruction of the major pulmonary arterial bed by organised thrombi.[24] Wolf et al.[26] found that 20% of CTEPH patients tested positive for aPL. An important study conducted by Martinuzzo et al.,[27] demonstrated higher rates of aPL positivity in patients with CTEPH compared with those with primary or secondary PH. Finally, aPL positive patients have a high-risk of PE, therefore the patients with CTEPH should be screened for thrombophilia, involving aPL (aCA, LAC).[8,18] Kanakis et al.[25] suggested that in patients with CTEPH, the presence of aPL would classify them as having APS, if they meet the clinical and laboratory criteria.

In patients with suspected PH the initial diagnostic tests include chest radiography, TTE, RHC, and pulmonary function tests. Ventilation perfusion lung scans are preferred over computed tomographic pulmonary angiography (CTPA) as the initial test because they detect CTEPH with greater sensitivity.[28]

CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME AND ACUTE RESPIRATORY DISTRESS SYNDROME

A small number of patients with APS (1%) develop a fulminant clinical presentation of catastrophic APS (CAPS). CAPS has a mortality rate of approximately 50% and comprises of with widespread multiple small blood vessel thrombosis, circulating aPL, and multi-organ infarction in days to weeks.[29,30] The main pulmonary complication of CAPS is acute respiratory distress syndrome (ARDS), with PE and alveolar haemorrhage occurring less commonly.[31]

ARDS is a severe life-threatening disease due to a known clinical insult, with new or worsening respiratory symptoms within 1 week: respiratory failure due to an infection or injury (not fully explained by cardiac failure or fluid overload) and refractory arterial hypoxaemia requiring supplemental oxygen treatment. ARDS can be categorised as mild, moderate, or severe, with mortality rates around 27%, 32%, and 45%, respectively. Radiographical findings include bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules.[32] The aetiology of ARDS in CAPS is unclear. In the acute phase of ARDS, the permeability of the alveolar-capillary membrane is increased, so proteinaceous oedema fluid, neutrophils, red blood cells, and immunoglobulins accumulate in the alveolar space.[33] In addition, pulmonary microembolism may cause vascular injury and elevated transport of proteins through the pulmonary microvascular barrier in the parenchyma.[34] aPL have also been found in the bronchoalveolarlavage (BAL) fluid of a patient with ARDS and APS. These results support the hypothesis that aPL could promote the process of ARDS in CAPS patients.[35]

DIFFUSE ALVEOLAR HAEMORRHAGE AND PULMONARY CAPILLARITIS

DAH is a syndrome of the lungs characterised by bleeding into the alveolar spaces, due to disruption of the alveolar-capillary basement membrane. This deterioration is caused by injury or inflammation of the arterioles, venules, or alveolar septal (alveolar wall or interstitial) capillaries.[36] Haemoptysis is the most common presenting symptom although it is absent in 33% of cases, even when haemorrhaging is severe. It is common for patients to initially present with cough, haemoptysis, fever, dyspnoea, and pleuritic chest pain. DAH may cause acute severe respiratory distress, requiring immediate ventilatory support with mechanical ventilation.[31]

Laboratory findings often demonstrate anaemia and elevated white blood cell count, but these are not essential to the diagnosis. Coagulation abnormalities should be excluded by checking a platelet count, prothrombin time, international normalised ratio, and partial thromboplastin time.[36] Chest radiographs usually show bilateral alveolar infiltrates, however the changes can be subtle, thus abnormalities are more reliably detected with computed tomography scanning.[37] Bronchoscopy and BAL, with or without biopsy, often aid in confirmation of the diagnosis. Diagnosis is characterised by increasing haemorrhagic appearance on serial BAL, serial increase in red blood cell counts, and presence of haemosiderin-laden macrophages in the BAL fluid.[38]

The exact incidence of DAH in patients with APS is unclear; it may be the initial manifestation of APS and a life-threatening situation. Yachoui et al.[39] found that DAH is a rare complication of primary APS that can also arise *de novo* in aPL positive individuals. Pulmonary capillaritis is one

of three different histopathological patterns seen in DAH and it appears to be the histopathological form occurring in APS patients with circulating aPL.[37] It is characterised by neutrophilic infiltration of the alveolar septum with associated oedema into the lung interstitium, causing structural necrosis, loss of capillary integrity, and haemorrhage.[40,41] Some authors observed that capillaritis does not appear to be the predominant pathology and believe that capillaritis in the setting of APS is likely an unrelated and coincidental phenomenon. Although this opinion is less frequently seen in literature, bland haemorrhage, another histopathological pattern of DAH, was found, rather than pulmonary capillaritis, in five out of six lung biopsies of APS patients.[39,42] Asherson and Greenblatt[43] also showed that alveolar haemorrhage and microvascular thrombosis could occur with or without pulmonary capillaritis in APS patients. Nonetheless, the most common trend is that capillaritis causes DAH in APS patients. In a case series, Cartin-Ceba et al.[44] found pulmonary capillaritis in three patient lung biopsies. Also, Deane and West[37] found DAH due to pulmonary capillaritis in the setting of high titres of aPL in four primary APS patients. They speculate that aPL can induce pulmonary capillaritis to tissue injury in non-thrombotic manifestations of primary APS, whilst thrombosis remains most common cause of lung injury. aPL cause upregulation of vascular endothelial cell adhesion molecules, therefore neutrophils are recruited and migrate into the alveolar septae with resulting tissue destruction and subsequently, extravasation of red blood cells occurs into the alveoli.[37]

The vasculitis/capillaritis leading to DAH may be limited to the lungs.[41] Most of the lung tissue may comprise small capillaries, allowing for greater contact between neutrophils and endothelial cells. Although unproven, this may be preferential to the binding of the β2GP1 antigen to endothelial cells, especially in the lung environment. It was reported that aPL can rarely lead to vasculitis in organs other than the lung.[45]

FIBROSING ALVEOLITIS

CFA (also called idiopathic pulmonary fibrosis) is a specific form of chronic, progressive, fibrosing, interstitial pneumonia of unknown cause, occurring in adults and limited to the lungs.[46] The literature regarding CFA as a rare pulmonary manifestation of APS is limited, however we were

able to identify three relevant studies. The first was a case report on a patient with primary APS who developed insidious diffuse pulmonary infiltrates.[47] The second was a case report of a patient with CFA, PE, and myocardial infarction in the presence of APS.[48] The third involved a cohort of 329 APS patients. It found significant associations between the presence of medium aCA immunoglobulin (Ig)G levels and medium β2GP1 IgM levels with CFA in APS patients (p=0.002 and p=0.00001, respectively). The correlation among CFA and IgG, aCA, and β2GP1 IgM levels supports the notion of a causative relationship between these types of circulating antibodies and such lesions. The number of patients with CFA was not mentioned in this latter example, limiting the extent of conclusions that can be drawn.[9]

POSTPARTUM SYNDROME

Postpartum syndrome is a distinctly rare clinical pulmonary manifestation of APS and in the setting of aPL is an entity reported only twice in the medical literature. In the first report, Kochenour et al.[49] detected three patients with postpartum syndrome. The clinical features are characterised by pleuritis, cyclic fever, and dyspnoea. Diffuse, patchy pulmonary infiltrates and pleural effusions were found in the radiological evaluation. One patient was also found to have cardiomyopathy.[49] Kupferminc et al.[50] identified a postpartum woman who developed fever, pulmonary infiltrates, cardiac conduction defects, and renal insufficiency following severe pre-eclampsia.[50] These obstetric cases are predisposed to a catastrophic APS-like syndrome with multiorgan system dysfunction driven by microangiopathy, including pulmonary parenchyma and vessels. Since 1994, there have been no new patients described in the literature. Although unproven, there may be a lack of awareness about this syndrome, or these patients may be evaluated as CAPS.

MANAGEMENT OF PULMONARY MANIFESTATIONS IN ANTIPHOSPHOLIPID SYNDROME PATIENTS

The therapy for non-obstetric APS patients is largely the same regardless of whether the disorder is classified as primary APS or autoimmune disease-associated APS. The treatment must be individualised according to the patient's current

clinical status and recurrence of thrombotic events. CAPS patients have to be carefully observed and treated, often in an intensive care unit. Incidentally found serum aPL positive asymptomatic patients do not require specific treatment.

The therapy for PE is the same in patients with APS as in the general population. The mainstay of treatment for APS includes antithrombotic medications like low molecular weight heparin, unfractionated heparin, warfarin, and aspirin. Heparin is generally administered alongside warfarin until the international normalised ratio (INR) has been within the target range of 2.0–3.0 for 2 consecutive days.[51] After the first thromboembolic event, the optimal duration of anticoagulation is uncertain in APS. However, Ruiz-Irastorza et al.[52] recommended anticoagulation duration for 3–6 months, if it is the first venous event with a known transient precipitating factor and a non-diagnostic or low-risk aPL profile (an isolated, intermittently positive, low-to-medium titre aCA or aβ2GP1).

Somers et al.[53] followed 412 patients with first venous thromboembolic events, finding that in the presence of aPL, the risk of recurrent thrombosis was doubled at the end of 6 months of antithrombotic therapy (29% versus 14%). Therefore, for many patients lifelong therapy is prudent. Some studies suggest that aspirin alone has minimal or no benefit for the prevention of thrombotic APS manifestations in patients who have experienced previous events.[54,55] However, in another study they found that aspirin (81 mg/day) reduced the risk of thrombosis in aPL positive individuals. Hydroxychloroquine (HCQ) may have some benefit for complications in SLE associated with APS patients; although it is unproven whether they benefit from HCQ, the control of SLE, or through aPL-mediated thrombosis.[56]

In the case of treatment failure, if recurrent thrombotic events occur despite the target range of 2.0–3.0, there are some alternative treatments, such as increasing the target of INR (3.1–4.0) or adding low-dose aspirin, low molecular weight heparin, or HCQ.[52]

Recently, new oral anticoagulants (i.e. direct thrombin inhibitors and factor Xa inhibitors) can be considered in patients who are warfarin intolerant/allergic or have difficulties with anticoagulant control.[57,58] Rituximab can be tried for recurrent thrombosis, despite sufficient anticoagulation. Nalli et al.[59] also showed that rituximab was effective for noncriteria aPL clinical manifestations (i.e. thrombocytopenia and skin ulcers). Some studies reported that glucocorticosteroids and other immunosuppressive therapies such as azathioprine, cyclophosphamide, and methotrexate could decrease the titres of aPL, but do not seem to reduce thrombotic risk.[60,61]

Early diagnosis and aggressive therapy is essential to the management of CAPS, ARDS, and DAH because the mortality rates are high. Generally, the aim of CAPS treatment is to reduce thrombotic events and suppress cytokine cascade. The treatment of CAPS includes a combination of anticoagulants, systemic glucocorticoids, plasma exchange, and intravenous Ig (400 mg/kg/day for 5 days). Also, it is reported that intravenous Ig might prevent recurrent thrombotic events like PE in APS patients. High doses of systemic glucocorticoids, 1 mg/day methylprednisolone intravenously for 3 days, followed by oral or parenteral 1 mg/kg/day prednisone have been recommended for CAPS patients. Also, high doses of glucocorticoids may be useful in ARDS, pulmonary microthrombosis, and DAH. After cessation of the corticosteroids, DAH may recur; in this situation other immunomodulatory therapy such as cyclophosphamide, cyclosporine, and mycophenolate should be used. Cyclophosphamide has also been used successfully in CAPS patients with SLE.[31,37,62-64] In management of ARDS patients, adding pulse cyclophosphamide and plasmapheresis to anticoagulation and a high-dose corticosteroid therapy may be required.[62]

In APS patients, pulmonary endarterectomy (PEA) is a choice for treatment of CTEPH. PEA requires careful assessment of the risks and benefits. It must be a multidisciplinary approach to limit the risk of thrombosis or bleeding and to manage possible thrombocytopenia.[8] Some studies recommended pulmonary arterial vasodilators such as bosentan and iloprost for patients with aPL-associated PH.[65,66] Inferior vena cava filters can be another treatment approach. Zifman et al.[67] identified 10 patients with APS and recurrent thrombotic events. They underwent inferior vena cava placement; 5 of the 10 patients died, 2 of them suddenly, and PE could not be excluded.

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