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CASE STUDY

Diffuse microvascular pulmonary thrombosis associated with primary antiphospholipid antibody syndrome

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Diffuse microvascular pulmonary thrombosis associated with primary antiphospholipid antibody syndrome. M. Maggiorini, A. Knoblauch, J. Schneider, E.W. Russi. ©ERS Journals Ltd 1997.

ABSTRACT: Thromboembolism is a well-known complication of the hypercoagulable state associated with anitphospholipid (aPL) antibodies. Acute respiratory failure (ARF) with diffuse pulmonary infiltrates has been reported in only a few patients with aPL antibodies.

We describe a 49 year old patient with spiking fever, livedo reticularis, mild haemoptysis and ARF. Chest radiography revealed diffuse bilateral pulmonary infiltrates, and high resolution computed tomography (CT) revealed patchy distribution of areas of ground-glass attenuations. Pulmonary emboli were excluded with angiography. Lung biopsy revealed diffuse microvascular thrombosis, without capillaritis. High serum levels of anticardiolipin (aCL) antibodies were found. The patient's condition improved dramatically after intravenous infection of 1 g methylprednisolone on three consecutive days, followed by 50 mg prednisone orally.

The rapid improvement following the administration of glucocorticosteroids suggests that anticardiolipin associated microvascular thrombosis, without inflammatory lesions, may depend on an interference with β_2-glycoprotein I (β_2=GPI) by anticardiolipin.

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Shortly after the development of the anticardiolipin (aCL) assay [1], it became apparent that antiphospholipid (aPL) antibodies, which include aCL antibodies and the lupus anticoagulant, were not limited to patients with lupus erythematosus but could be found in persons without this autoimmune disease. The aPL antibodies associated hypercoagulable state has been termed the "antiphospholipid thrombosis syndrome". In the aCL antibody thrombosis syndrome, thromboses of the arteries are almost as common as venous thrombotic events [2, 3]. This syndrome occurs without underlying diseases (primary), as well as secondary to an underlying disease such as lupus erythematosus or another autoimmune disorder, malignancies, infections, systemic inflammation, or ingestion of drugs. The primary type is much more common than the secondary [2].

The most common pulmonary manifestation of the aPL syndrome are pulmonary embolism, and pulmonary hypertension secondary to recurrent pulmonary emboli [4]. Only a few patients with pulmonary infiltrates, spiking temperature and severe respiratory failure associated with aCL antibody syndrome have been reported, and exclusively in the rheumatological literature [5–10]. We describe a patient with primary aCL antibody syndrome, who developed an adult respiratory distress syndrome (ARDS)-like clinical picture and who improved dramatically after high-dose intravenous glucocorticosteroid treatment.

Case report

A 49 year old man was admitted to hospital because of recurrent livedo reticularis of the fingers and toes, fever, cough with occasional mild haemoptysis, and shortness of breath at rest and at minimal exercise. For 2–3 yrs he had suffered from cerebral transient ischaemic attacks and recurrent painful acrocyanosis of the toes and fingers. The oscillogram of the peripheral arteries was normal. Capillary microscopy showed a slightly decreased density of the capillaries of the toes. Five months prior to admission, the patient developed acute fever, dyspnoea, a dry cough with occasional slightly bloody expetorations, and an incapacitating weakness. A chest radiogram showed bilateral patchy infiltrates. He was treated with clarithromycin. Two months prior to admission, a deep venous thrombosis of the left leg was detected. Lung perfusion and ventilation scan indicated low probability for pulmonary embolism. The patient received oral anticoagulation with phenprocoumon.

On admission, the obese patient (body mass index (BMI) 36 $kg \cdot m^{-2}$) had a temperature of 37.4°C and a heart rate of 104 $beats \cdot min^{-1}$. His blood pressure was 115/80 mmHg, and respiratory rate 18 $breaths \cdot min^{-1}$. His toes and fingers were cold and showed a painful livedo reticularis. Four necrotic cutaneous lesions, 5×5 mm in diameter were present on the right foot. An electrocardiogram (ECG) was normal.

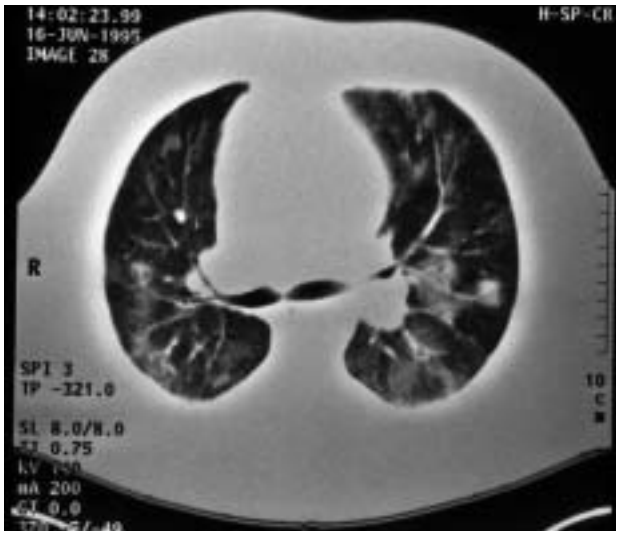

Fig. 1. – High resolution computed tomography (CT) scan demonstrating bilateral perihilar and peripherally located patchy distributed areas of ground-glass attenuation.

Chest radiography showed a normal sized heart and bilateral patchy infiltrates. A high resolution computed tomography (CT) scan revealed bilateral patchy areas of ground-glass attenuation (fig. 1). Pulmonary angiography revealed moderately dilated central pulmonary arteries but no pulmonary emboli.

Forced vital capacity (FVC) was 92% predicted, and forced expiratory volume in one second (FEV_1) 88% pred. Transfer factor for carbon monoxide ($T_{L,CO}$) was 87% pred. Arterial blood gas values documented severe hypoxaemia: oxyhaemoglobin (HbO_2) 78%; arterial oxygen tension (P_{a,O_2}) 5.7 kPa; arterial carbon dioxide tension (P_{a,CO_2}) 5.2 kPa; and pH 7.38.

Right heart catheterization showed a pulmonary artery pressure of 31/18 mmHg, the mean pulmonary artery occlusion pressure was 8 mmHg, and the estimated mean pulmonary capillary pressure was 12 mmHg, determined by analysis of the pulmonary artery occlusion pressure curve decay [11]. The cardiac index was 4.0 $L \cdot min^{-1} \cdot m^2$ (thermodilution). Transoesophageal echocardiography showed normal left and right ventricular function, and a slight thickening of the aortic and mitral valves. No intraventricular or atrial thrombi could be detected.

Duplex and pulsed-wave doppler sonography of the extracranial arteries and transcranial doppler sonography of the intracranial arteries were normal. Magnetic resonance tomography of the brain revealed a few small hypodensities in the left thalamus and in the basal areas of both cerebellar hemispheres, consistent with small cerebral and infarcts.

Anticardiolipin- immunoglobulin G (IgG) was 0.676 $E \cdot L^{-1}$ (normal 0–0.01 $E \cdot L^{-1}$), aCL-immunoglobulin M (IgM) 0.021 $E \cdot L^{-1}$ (normal 0–0.01 $E \cdot L^{-1}$) and aCL-immunoglobulin A (IgA) 0.026 $E \cdot L^{-1}$ (normal 0–0.01 $E \cdot L^{-1}$) Serum levels of antithrombin III, protein-S and protein-C were normal. Partial thromboplastin time was 63 s, and fibrinogen 5.8 $g \cdot L^{-1}$. Antinuclear antibodies, antideoxyribonucleic acid (DNA) antibodies, antineutrophil cytoplasmic antibodies, antiglomerular basal membrane anti-bodies and the rheumatoid factor were negative.

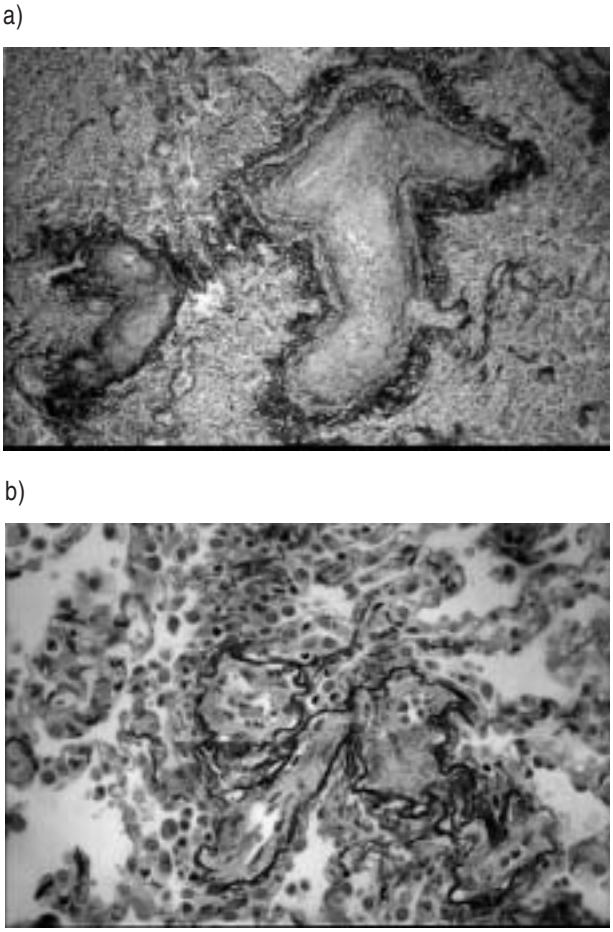

Fig. 2. – Photomicrographs of lung biopsy showing: a) Small muscular artery (diameter 300 µm) presenting with hypertrophy of the media and a proliferation of the intima, in the absence of inflammatory cells, which narrows the arterial lumen to a considerable extent; b) small arterioles (diameter 50–100 µm) presenting with proliferation of the smooth muscle fibres. (Van Gieson-elastin stain; internal scale bar = 100 µm).

Haemoglobin value was 111 $g \cdot L^{-1}$, polymorphonuclear (PMN) leucocytes 5.5×10^9 $cells \cdot L^{-1}$ and the number of thrombocytes 120×10^9 $cells \cdot L^{-1}$.

Cultures of bronchoalveolar lavage (BAL) fluid remained sterile. A large lung biopsy was taken from the middle lobe by video-assisted thoracoscopy. Histology of the specimen revealed thickened pulmonary arteriole walls, with hypertrophy of the medial layer and an enlarged intimal layer, which presented with an increased number of fibroblasts, elastic fibres and smooth muscle cells, but without any inflammatory cells (fig. 2). The internal lumen of the majority of the arterioles and of the capillaries was occluded by thrombi. The pulmonary veins were normal. The lumen of the alveoli contained pigmented macrophages, erythrocytes and PMNs. The interlobular septa were slightly thickened. Cultures of the biopsy specimen remained negative.

The patient received 1 g methylprednisolone intravenously on three consecutive days, followed by 50 mg prednisone *p.o.* daily. Heparin was given by the intravenous route in therapeutic doses. Within days, the patient's condition improved dramatically: the dyspnoea decreased, the fingers and toes became warm, the livedo reticularis regressed almost completely, and the pain

disappeared. The pulmonary infiltrates resolved. Twelve days later, arterial blood gas analysis (without oxygen) showed: HbO_2 96%; P_{a,O_2} 11.5 kPa; and P_{a,CO_2} 4.5 kPa. The patient, while using a bicycle ergometer was able to perform 25W, 50W, 100W and 125W for 3 min at each step. At the last step (150W) exercise was stopped after 2 min because of muscular fatigue in the legs.

Discussion

A 49 year old patient with a history of arterious and venous thrombosis developed respiratory failure with diffuse pulmonary infiltrates but with a normal pulmonary angiogram. Histological examination of lung tissue revealed thrombotic occlusions of arterioles and capillaries and no inflammatory lesions. High serum levels of aCL-IgG, -IgM and -IgA antibodies were found, but serology for lupus erythematosus was negative. These findings support the diagnosis of a primary aPL antibody syndrome [3], with aCL antibody-associated *in situ* microvascular thrombosis of the pulmonary circulation.

In the primary aCL antibody syndrome, arterial and venous thromboses are common. In a study including 70 patients, the incidence was 54 and 44%, respectively [3]. Less frequent is the combination of both, present in 14% of the patients in the above study. The most frequently reported pulmonary complication of the aPL antibody syndrome is pulmonary hypertension secondary to recurrent thromboembolism [4]. In the present patient, right heart catheterization revealed only mild pulmonary hypertension, although extensive thrombotic occlusion of the pulmonary arterioles were present.

Only a few cases of acute respiratory failure (ARF) associated with spiking fever, high serum levels of aCL antibodies and microvascular thrombosis with or without capillaritis and alveolar haemorrhage have been published, and exclusively in the rheumatological literature [5–10]. A total of 18 cases of aPL antibody-associated ARF and/or ARDS have been reported. Three of them became manifest postoperatively [8, 12], and four in the postpartum period [13, 14]. Of the remaining 11 cases, three were associated with the diagnosis of systemic lupus erythematosus [5, 15], and eight with the diagnosis of primary aCL antibody syndrome [6–10]. The eight cases admitted to the hospital with ARF associated with primary aCL antibody syndrome are summarized in table 1. The common symptoms and signs consisted of fever, dyspnoea, tachypnoea, hypoxaemia, and bilateral pulmonary infiltrates. Histological examination of lung

Table 1. – Clinical and histological findings in primary anticardiolipin antibody syndrome associated with pulmonary infiltrates on chest radiography

First author [Ref]	Pt No.	Age yrs	Sex	Clinical manifestations	Chest radiographic findings	Lung biopsy/autopsy			Treatment	Improved
						Microvascular thrombosis	Alveolar haemorrhage	Pulmonary capillaritis		
HILLERDAL [7]	1	43	M	Myocardial infarction cerebrovascular accident	Pulmonary infiltrates	-	+	-	Corticosteroids/ cyclophosphamide	Yes
	2	42	M	Arterial thrombosis	Diffuse pulmonary infiltrates	NA	NA	NA	Corticosteroids/ cyclophosphamide	Yes
GERTNER [6]	1	47	M	Seizures, DVT, myocardial infarction	Diffuse pulmonary infiltrates	-	+	+	Corticosteroids	Yes
	2	21	F	Cerebrovascular accident, foetal loss	Consolidation of the left lung	+	-	-	-	NA
	3	41	M	Livedo reticularis, cerebrovascular accidents, seizures, adrenal insufficiency	Interstitial and alveolar infiltrates	+	+	+	Corticosteroids	Yes
GHOSH [8]	1	43	F	DVT, AV-block III, cardiac arrest	Diffuse pulmonary infiltrates	+	+	-	-	Died
SAVIN [10]	1	41	M	Cerebrovascular accident	Nodular infiltrates	-	+	+	Corticosteroids	Yes
CRAUSMAN [9]	1	56	F	DVT, cerebrovascular accident	Alveolar infiltrates	-	+	+	Corticosteroids/ cyclophosphamide	Yes

Pt: patient; DVT: deep vein thrombosis; AV: atrioventricular; NA: information not available.

specimens, obtained in 7 of the 8 patients (by biopsy or at alveolar haemorrhage in six; and pulmonary capillaritis in four. All patients who were treated with corticosteroid improved, regardless of additional treatment with cyclophosphamide. It is possible that, at least in part, the rapid improvement in gas exchange and the quick radiological resolution of the pulmonary infiltrates was a consequence of the reabsorption of alveolar haemorrhage. In fact, alveolar bleeding secondary to microvascular thrombosis is most likely the substrate of the patchy pulmonary infiltrates seen in the present patient and those of others [6, 8].

The aCL antibody-associated ARF may also be accompanied by acute dysfunction of multiple other organs [5, 13, 14], and is called the "catastrophic antiphospholipid syndrome" (CAS) [16]. The clinical profile of 10 patients with the CAS, reviewed by ASHERTON, [16] nine with a systemic lupus erythematosus and one with the primary aCL antibody syndrome, was characterized by: renal dysfunction and central nervous system symptomatology in nine cases; malignant systemic hypertension and skin manifestations in seven; and an ARDS in two.

Little is known of the mechanism by which aCL antibodies are involved in the pathogenesis of microvascular thrombosis leading to ARF. The aCL antibodies exhibit an affinity for phospholipids involved in many steps of the haemostasis system. In order to bind phospholipids, aCL antibodies require serum co-factor β_2-glycoprotein I (β_2-GPI) [2, 17]. It has been suggested that primary aCL antibody syndrome-associated lesions, even in the absence of inflammation, may be attributed to blood flow stagnation analogous to aCL antibody-associated dermal vessel thrombosis [2, 5, 18]. The results of recent studies suggest that the procoagulant action of aPL antibodies may interfere with endothelial release of prostacyclin, based on the interference with different coagulation proteins, such as protein-C or -S, thrombomodulin and antithrombin-III, as well as on interference with platelet activation [2, 17]. In addition, it has been reported that patients with Sneddon's syndrome, which is defined by the occurence of generalized livedo reticularis together with recurrent cerebral transient ischaemic attacks, may show aCL antibodies which bind to cardiolipin only in the presence of β_2-GPI [19]. This suggests that an interference with β_2 GPI by aCL, which acts as an anti-β_2-GPI antibody, may play a pathogenic role in thrombotic lesions associated with the aCL antibody syndrome.

We speculate that the microvascular thromboses without inflammatory lesions in the present patient and patient No. 2 reported by GERTNER and LIE [6] (table 1) could be associated with the presence of aCL antibodies with an anti-β_2-GPI activity. Because the patient studied improved rapidly following administration of glucocorticosteroids, we suggest that patients with a primary aCL antibody syndrome be treated with glucocorticosteroids, even in the absence of pulmonary capillaritis in the lung biopsy. However, surgical lung biopsy is not without risks in patients like this. Thus, in patients known to have anticardiolipin antibody, who have no other aetiologies for diffuse pulmonary infiltrates (*e.g.* infection), glucocorticosteroids should be initiated immediately and without a lung biopsy.

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