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Case report

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Primary antiphospholipid syndrome with refractory alveolar hemorrhage and severe mitral regurgitation: a case report and literature review

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Summary

The antiphospholipid syndrome (APS) is a hematological disorder that presents a state of hypercoagulability of autoimmune origin, characterized by thrombotic venous and / or arterial thrombosis, recurrent fetal loss and antiphospholipid antibodies presence. Another manifestation of this disease is diffuse alveolar hemorrhage, clinical entity that may occur with adult respiratory distress syndrome, respiratory failure and high mortality. Among its causes, we find lupus erythematosus, Behcet's disease, microscopic polyarteritis, cryoglobulinemia vasculitis, Goodpasture's syndrome, and granulomatous vasculitis. The differential diagnosis in a patient with severe valvular disease secondary to APS is a clinical challenge.

We report a case of a 31-year-old woman, diagnosed with primary antiphospholipid syndrome with severe mitral regurgitation, who presented three episodes of diffuse alveolar hemorrhage, refractory to medical management. The case is discussed and a literature review is performed.

Key words: antiphospholipid syndrome, alveolar hemorrhage, mitral regurgitation

Síndrome antifosfolípido primario con hemorragia alveolar refractaria e insuficiencia mitral severa: reporte de un caso y revisión de la literatura

Resumen

El síndrome antifosfolípido (SAF)es un trastorno hematológico que cursa con un estado de hipercoagulabilidad de origen autoinmune, caracterizado por fenómenos trombóticos venosos o arteriales, pérdidas fetales recurrentes y presencia de anticuerpos antifosfolípidos. Otra manifestación de esta patología es la hemorragia alveolar difusa (HAD), entidad clínica que puede cursar con síndrome de dificultad respiratoria del adulto, falla ventilatoria y alta mortalidad. Entre sus causas se encuentran lupus eritematoso, enfermedad de Behcet, poliarteritis microscópica, vasculitis por crioglobulinemia, síndrome de Goodpasture y vasculitis granulomatosa. El diagnóstico diferencial en un paciente con enfermedad valvular severa secundaria aSAF es un reto clínico.

Reportamos el caso de una mujer de 31 años con diagnóstico de SAF primario con insuficiencia mitral severa, quien presento 3 episodios de HAD refractaria al manejo médico. Se discute el caso y realizamos una revisión de la literatura.

Palabras clave: síndrome antifosfolípido, hemorragia alveolar, insuficiencia mitral.

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Caso report

A 31-year-old female diagnosed with primary antiphospholipid syndrome for having a history of multiple arterial and venous thrombotic events (pulmonary thromboembolism as an initial manifestation, deep venous thrombosis in the lower limbs, and ischemic cerebrovascular stroke) with lupus anticoagulant positivity, IgG Anticardiolipin and B2 glycoprotein. Prior to admission to our institution, she presented diffuse alveolar hemorrhage, which required intrahospital management with plasmapheresis, corticosteroid pulses and the first dose of cyclophosphamide.

The patient was admitted to the hospital with a clinic picture of a 3-day cough with hemoptoid expectoration, associated with dyspnoea, pain in the right hemithorax, without febrile spikes. Among her antecedents, she had primary antiphospholipid syndrome diagnosed at age 20, moderate mitral insufficiency, therapeutic failure to warfarin, under treatment with enoxaparin, prednisolone, and inferior vena cava filter. At physical examination, she was in poor general condition, with signs of respiratory distress, supraclavicular retractions, cardiac sounds with systolic murmur in the mitral focus, respiratory sounds with crackles in both lung bases and grade I edema in extremities.

The hemogram showed anemia and thrombocytopenia, with no leukocytosis, preserved renal function, normal C3 and C4 complement, negative ANA, strongly positive IgG anticardiolipin, negative cANCA and pANCA (Table 1). Chest x-ray showed diffuse alveolar occupation. (Figure 1), finding confirmed by computerized axial tomography. (Figure 2)

The patient presented respiratory failure requiring invasive respiratory support. Fibrobronchoscopy was performed with alveolar bronchoalveolar lavage. There was evidence of hemorrhagic fluid, Giemsa stain, Ziehl Neelsen stain, Grocott stain negative for pneumocystis, alcohol-resistant bacilli and fungi, negative cultures for mycobacteria, cytology with predominance of macrophages and neutrophils, Prussian blue stain documented 85% of hemosiderophages. Figure 3

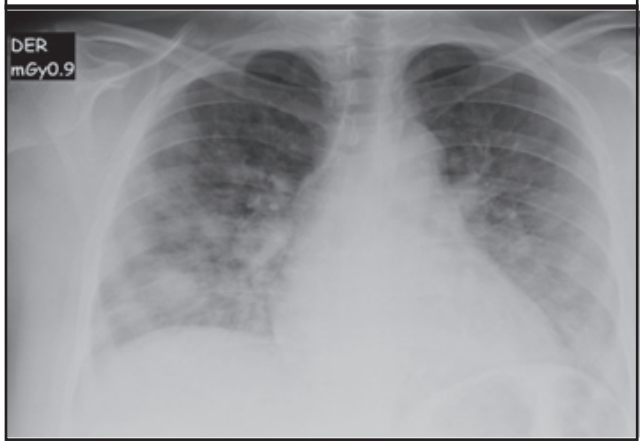
Table. 1 Paraclinics

Paraclínicos

PARACLINICO	04/07/12	29/10/14	05/11/14
LEUCOCITOS	11200	8500	7600
HB - HTO	6.9 - 19	9.2 - 26	8.4 -24
PLAQUETAS	60000	120000	45000
PT – PT CONTROL	11 (10.4)	10.4 (10.2)	12
PTT – PTT CONTROL	36 (30.4)	33 (30.6)	34
C3 – C4	91 - 24	106 – 23	72- 27
ANTICARDIOLIPINA IGG mcg	300	12.4	24
ANTICARDIOLIPINA IGM mcg	23	3	4.7
ANTI DNA	NEGATIVO	NEGATIVO	NEGATIVO
ANAS	NEGATIVO	NEGATIVO	NEGATIVO
pANCA, cANCA	NEGATIVO		
CREATININA	1.4	1.3	1.2
BUN	24	22	23

Figure 1.

Chest X-ray: Diffuse alveolar occupation. Bilateral multilobar consolidation of central and basal predominance.



Based on the results obtained, diffuse alveolar hemorrhage was diagnosed. She received treatment with pulses of methylprednisolone and cyclophosphamide, with resolution of respiratory symptoms, stabilization of hemoglobin and decrease of pulmonary infiltrates. Later, she presents respiratory deterioration associated with hemoptysis and anemization, with radiological finding of opacities of alveolar occupa-

Figure 2.

Chest CAT: Findings of bilateral alveolar occupation compatible with diffuse alveolar hemorrhage.

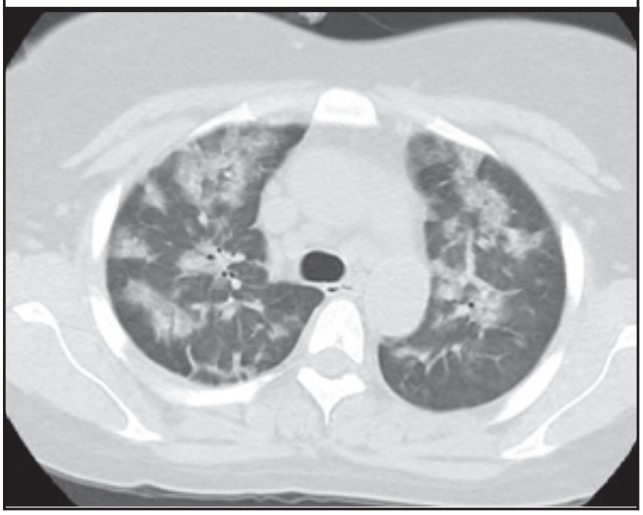
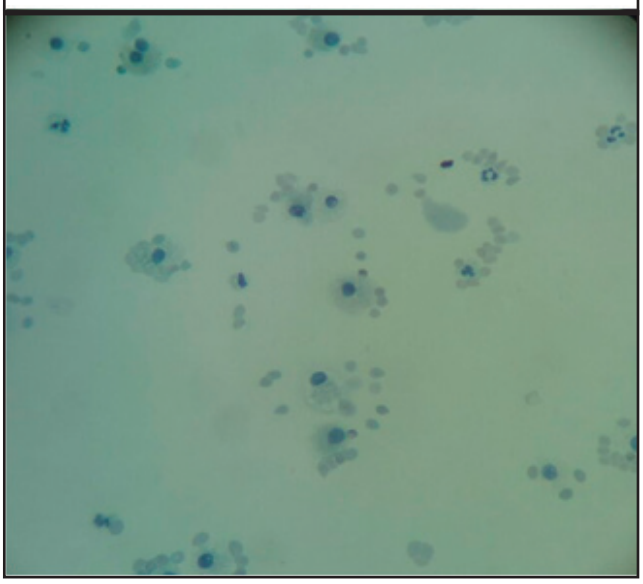


Figure 3.

Prussian blue shows hemosiderin-loaded macrophages.



tion. Considering a new event of alveolar hemorrhage, daily plasmapheresis is started, completing a total of 14 sessions without complications. She presented satisfactory evolution, clinical resolution, radiological improvement. Plasmapheresis is suspended and there is a relapse of alveolar hemorrhage, anemia, thrombocytopenia, which requires non-invasive ventilatory support and resumption of plasmapheresis sessions. ADAMS 13 is performed with 79% activity, marrow biopsy shows no evidence of microthrombosis, and transbronchial biopsy observes capillaritis. Refractory alveolar hemorrhage is determined, and Rituximab 500 mg iv is administered weekly for 4 weeks.

After weeks with no symptoms, the patient presents dyspnea, edema in the lower limbs, increased oxygen requirements, diffuse alveolar infiltrates on chest X-ray in four quadrants. However, she presents no anemia, no thrombocytopenia, no Hemoptysis. With the immunosuppressive therapy received, a transesophageal echocardiogram is performed, demonstrating severe mitral insufficiency, with marantic characteristics, with decreased ejection fraction and increased pro BNP. She receives medical management for heart failure with loop diuretic, beta blocker, angiotensin converting enzyme inhibitor and spironolactone. She presented clinical improvement; no surgical treatment of severe mitral regurgitation is performed. The treatment is completed with cyclophosphamide for 6 months; corticoid, anticoagulation, and management for permanent cardiac failure, with satisfactory evolution without a new episode of alveolar hemorrhage.

DISCUSSION

Alveolar hemorrhage is a manifestation that occurs in the minority of patients with primary APS, mainly described in antiphospholipid syndromes secondary to systemic erythematosus lupus (1). In the absence of aggressive immunosuppressive therapy, it is associated with high morbidity and mortality. (1)

The initial clinical manifestation presented by the patient was cough, dyspnea and hemoptysis, similar to that reported in the literature (1-3). Radiography as well as thoracic CAT showed, as the main finding, an increase in the density of the pulmonary parenchyma of diffuse alveolar distribution in both lung fields, as evidenced in previous cases (1,2). Radiological findings are not specific to this entity and may vary in the course of disease (4).

In a series of case reports, the presentation of diffuse alveolar hemorrhage with primary APS was associated with strongly positive IgG anticardiolipin titers, as in our clinical case (1). Laboratory studies frequently demonstrate anemia as a marker of pulmonary blood loss (4), and thrombocytopenia as a marker of APS activity (1). The diagnosis of alveolar hemorrhage was focused under clinical suspicion and confirmed by fibrobrocoscopy with the presence of alveolar blood, and 85% of hemocenterophages. The transbronchial biopsy is a suboptimal examination for DAH diagnose, given its poor performance and that its findings may not be representative of the entire lung (4). In our patient there was no evidence of capillaritis. According to Cartin-Ceba in a series of cases of patients with primary APS taken to open lung biopsy, soft hemorrhage was the main pathological finding, over capillaritis (1).

One-third of patients with primary APS have valvular abnormalities, with left valve predilection (5). In this case, severe mitral insufficiency associated with heart failure with decreased ejection fraction and alveolar hemorrhage were documented. In a study of 18 patients with primary APS and DAH, 22% had a history of heart failure (1), suggesting that both pathologies may occur simultaneously and require a comprehensive treatment, as the individual management of each entity may lead to deterioration of the patient.

As in reported cases, the patient was initially treated with high doses of steroids (1,6) and early management of corticosteroid-sparing immunosuppressants such as cyclophosphamide, plus plasmapheresis were performed daily (1,3,5). However, when these were discontinued for 48 hours, the patient's clinical picture worsened and Rituximab therapy was added in combination with cyclophosphamide, as in a report of 3 patients in the series at Clínica de Mayo, obtaining until now an adequate clinical response. This therapeutic option should be considered in patients with refractoriness to the initial management (7). In other series, azathioprine was used with unfavorable results (1,3).

Given the rarity of primary APS with refractory alveolar hemorrhage and severe mitral insufficiency that do not improve with conventional treatment, it is of paramount importance to suspect associated pathologies such as heart failure in order to provide an integral treatment.

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