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Catastrophic antiphospholipid syndrome associated with crescentic glomerulonephritis: A clinicopathologic case

M. Cisternas[1], M.A. Gutiérrez[1], H. Rosenberg[2], A. Jara[3], S. Jacobelli[1]

Departments of Clinical Immunology and Rheumatology[1], Pathology[2], and Nephrology[3], Escuela de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile.

Marcela Cisternas, MD, Fellow in Rheumatology; Miguel A. Gutiérrez, MD, Assistant Professor; Helmar Rosenberg, Professor of Pathology; Aquiles Jara, MD, Assistant Professor; Sergio Jacobelli, MD, Professor of Medicine, Chief of Dept. of Clinical Immunology and Rheumatology.

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Please address correspondence and reprint requests to: Dr. Miguel A. Gutiérrez, Depto. Inmunología Clínica y Reumatología, Pontificia Universidad Católica de Chile, Marcoleta 367-Casilla 114-D-, Santiago, Chile.
E-mail: gutierre@med.puc.cl

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ABSTRACT

The association of renal failure with catastrophic antiphospholipid syndrome has been reported in the context of microvascular occlusions and/or malignant hypertension. We describe a 36-year-old woman who died of multiorgan failure with the laboratory, clinical and histopathological characteristics of catastrophic antiphospholipid syndrome associated with a crescentic glomerulonephritis and renal failure.

Introduction

The primary antiphospholipid syndrome (PAPS) is now well established as an entity defined by thrombotic phenomena, recurrent abortions, or thrombocytopenia and positive serum antiphospholipid antibodies, in the absence of an underlying disease (1). The spectrum of clinical manifestations has been expanded since its initial description, and now includes neurological, hematological, cardiac and cutaneous involvement (2). Compared with other manifestations, renal involvement has been little discussed in the literature, however.

There is a particular presentation that is called catastrophic antiphospholipid syndrome (CAPS), because it is a devastating syndrome characterized by multiple vascular occlusion, often resulting in death (3). We describe a patient with CAPS in association with crescentic glomerulonephritis, without evidence of systemic lupus erythematosus (SLE).

Case report

A 36-year-old woman was admitted to our hospital in March 1995 because of progressive asthenia and fatigue. A year earlier she had a deep vein thrombosis in her right leg, and was placed on oral anticoagulation treatment with a target INR unknown to us because she was followed in another hospital. She had had 2 successful pregnancies in the past with no fetal loss. Two weeks before admission to our hospital she had stopped the anticoagulant because of gynecological bleeding.

Upon examination the patient was pale, tachycardic (138/min), and normotensive (140/75). Laboratory tests showed a hematocrit of 15%, with marked microcytosis and hypochromia; normal platelet and white cell counts; erythrocyte sedimentation rate (ESR) 88 mm/hr; blood urea nitrogen 18 mg/dl, and creatinine 1.75 mg/dl. Urine culture was positive for *Escherichia coli.* She was transfused with 3 units of red cell pack, placed on treatment with Ciprofloxacine 1 gr PO/day and oral iron, and discharged.

Two weeks later the patient presented with polyarthralgias and consulted our outpatient clinic. Laboratory tests demonstrated renal failure with creatinine 3.2 mg/dl, proteinuria 7.6 gr/day, and a urine sediment with hematuria and hyaline and granular casts. She progressively developed respiratory failure associated with hemoptoic sputum, fever, oliguria and generalized edema. She was finally admitted to the intensive care unit. Her laboratory tests showed: blood urea nitrogen 71 mg/dl, creatinine 11.2 mg/dl, hematocrit 26.1%, ESR 88 mm/hr, PaO_2 54 mm Hg, $PaCO_2$ 24 mm Hg, pH 7.33 U, bicarbonate 12 mEq/lt. Chest x-rays revealed extensive bronchopneumonia. Blood cultures were positive for *Staphylococcus aureus.*

It was necessary to place the patient on mechanical ventilation, daily hemodialysis, vasoactive drugs and antibiotics. Antinuclear antibodies were positive at titers of 1/200. A direct Coombs test was positive. The anti-ds-DNA, anti-Ro/La anti-RNP/Sm, anti-Scl-70, and anti-neutrophil cytoplasmic antibodies (ANCA) were all negative; C3 and C4 complements were normal. She received high dose corticosteroids (3 gr intravenous methylpredisolone). Despite aggressive treatment she developed refractory shock and died 8 days after her second admission to the hospital.

Post-mortem we obtained positive IgG antiphospholipid antibody titers (95.1 GPL, normal value in our laboratory <15 GPL), while IgM antiphospholipid antibodies were negative (APhL ELISA Kit, Louisville APL Diagnostics Inc., Louisville, KY). Lupus anticoagulant was also positive. Later, the patient's serum was tested for anti β_2-glycoprotein-I antibodies, and was found to be positive for the IgG (151 units, NV < 20 units) and negative for the IgM isotypes (QUANTA Lite ELISA kit, INOVA, San Diego, CA).

Autopsy revealed non-inflammatory

thrombotic microangiopathy in the kidneys (Fig. 1), large intestine, pancreas, spleen, adrenals, thyroid, muscles, peripheral nerves, lungs and heart with microinfarcts (Fig. 2). Leg thrombophlebitis and mitral valve non-infectious fibrinous thrombosis were found. Cellular, fibrocellular and fibrous crescentic glomerulonephritis with 87% crescents were detected, with negative immunofluorescence for C3, C1q, IgA and IgM, and with fibrin in some crescents (Fig. 3). No dense deposits were seen on electron microscopy. There was extensive, bilateral acute, chronic bronchopneumonia with distressed lungs. There was no evidence of vasculitis in any organ. The final autopsy conclusion was catastrophic antiphospholipid syndrome and crescentic glomerulonephritis.

Discussion

Since the first description of CAPS by Asherson in 1992 (3), an increasing number of patients with this syndrome have been reported with a mortality rate of over 50% (4).

The diagnosis of CAPS in our patient was established post-mortem. She had a history of leg thrombophlebitis, the acute and accelerated involvement of multiple organs, and findings of multiple vascular thrombosis on necropsy, with the presence of anticardiolipins, anti-β_2-glycoprotein-I antibodies, and lupus anticoagulant (3). As has been reported in most cases of CAPS, there is a suspected trigger for the thrombotic event (4), which in this case seemed to be the interruption of the anticoagulation treatment a few weeks before.

Renal histology showed crescentic glomerulonephritis with negative immunofluorescense and the absence of dense deposits on electron microscopy. Although she had positive antinuclear antibodies, and the diagnosis of SLE was considered during her hospitalization, she did not meet the criteria for SLE or for any other connective tissue disease. Necropsy also failed to show any findings supporting the diagnosis of SLE or vasculitis.

Renal involvement has been described in more than 70% of patients with CAPS, accompanied in most cases by hypertension, which often proved fatal (4). The majority of patients presented evidence of renal damage on routine blood testing or urinalysis. Histopathological studies have demonstrated thrombotic disease of the glomerular capillaries and small renal arteries, with no evidence of active glomerulonephritis (4-8). Renal infarctions were also documented in some patients (9). The association of primary CAPS with crescentic glomerulonephritis has not been reported before. In patients with "simple" PAPS, renal in-

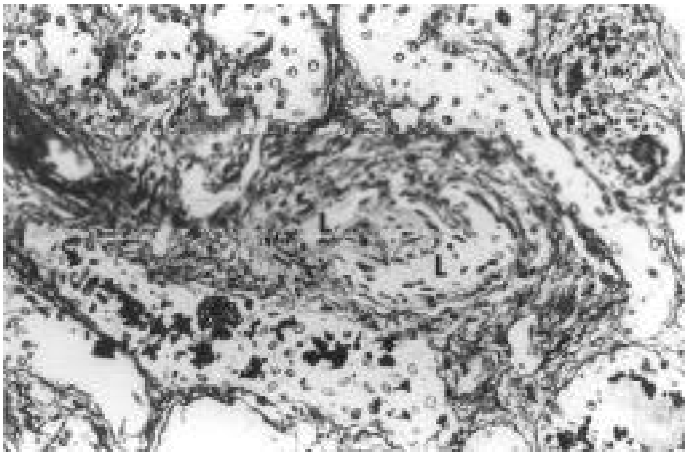

Fig. 1. Organized thrombus with recanalization (L) in a renal cortical radial artery. Silver metenamine x 200.

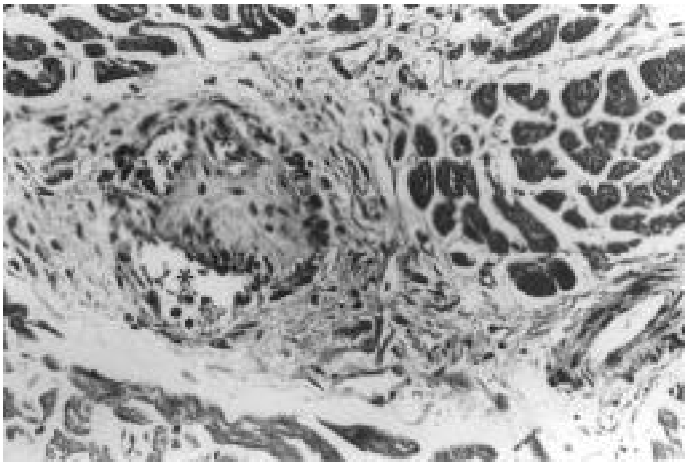

Fig. 2. Branch of a coronary artery in the left ventriculum wall that displays 3 lumens (*) consistent with organized thrombus with recanalization. The perivascular area has lax fibrosis. Hematoxilin-eosin x 200.

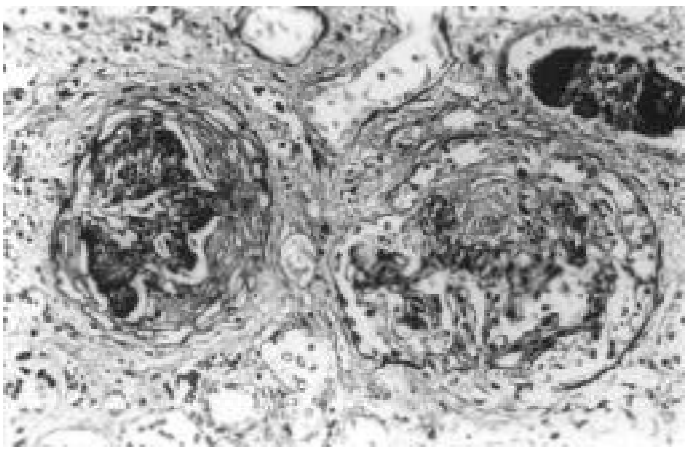

Fig. 3. Renal glomerulus with extensive cellular crescents (➔) and another with delamination of the Bowman parietal capsule and fibrocellular glomerulo-capsular proliferation. Silver-metenamine x 200.

volvement has been documented in approximately 25% of cases, and its clinical and pathological characteristics are variable (10). Similarly to CAPS, thrombotic microangiopathy in the nephrovascular area is the most frequent pathological lesion observed (10-12). Exceptionally, focal proliferative glomerulonephritis without any sign of glomerular thrombosis has also been described in a child (13).

The crescentic glomerulonephritis in our patient corresponds to pauci-immune crescentic nephritis. This category includes patients with systemic vasculitis as well as "idiopathic" isolated crescentic nephritis (14). The presence of ANCA in many patients with apparently isolated crescentic nephritis suggests that this represents a renal-limited form of vasculitis (15). However, in our patient the absence of ANCA and the lack of histopathologic evidence of vasculitis exclude this diagnosis.

Thrombotic microangiopathy has been described in many conditions with renal involvement (16), but is extremely rare in crescentic nephritis. We found a single report describing the association of ANCA-positive crescentic glomerulonephritis and thrombotic microangiopathy, but the antiphospholipid antibodies status of the patient was not reported (17). Our case represents, to the best of our knowledge, the first description of an association of primary CAPS with crescentic glomerulonephritis, suggesting that crescentic glomerulonephritis could in some cases represent a complication of antiphospholipid antibodies.

It is now recognized that the extent and type of a glomerular lesion depends on the cell types that accumulate in the glomerulus. Although the accumulation of neutrophils alone results in acute injury and dysfunction with intense cell proliferation, it does not lead to crescent formation. In contrast, the accumulation of monocytes/macrophages and T cells results in damage to the glomerular wall, fibrin formation in the Bowman's space, and crescent formation. Furthermore, it has been recently demonstrated in an animal model that the neutralization of the receptor CX3CR1 for the T-cell and monocyte/macrophage chemokine, fractalkine, could prevent crescentic glomerulonephritis (18). Simantov *et al.* demonstrated the activation of the vascular endothelium by anticardiolipin antibodies, resulting in the increased binding of monocytes (19). The authors found that incubation of human umbilical vein endothelial cells with IgG from patients with anticardiolipin antibodies induced a 2- to 3-fold increase in monocyte adhesion over that seen in endothelial cells incubated with IgG from normal subjects. Moreover, it was demonstrated that β_2-glycoprotein I played a role as a cofactor for antiphospholipid antibodies. An interesting finding is that the highest level of endothelial cell activation was induced by anticardiolipin antibodies from patients with primary antiphospholipid syndrome. Whether this mechanism, anticardiolipin antibodies-induced monocyte activation, is actually implicated in the crescent formation associated with catastrophic antiphospholipid syndrome remains to be studied.

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