ANCA-associated vasculitis and Igg4-related disease: An overlap syndrome or two distinct diseases?

Vasculitis ANCA positivas y Enfermedad relacionada con IgG4: ¿un síndrome de superposición o dos enfermedades distintas?

Dear Editor,

The ANCA-associated vasculitis (AAV) is typically characterized by pauci-immune crescentic glomerulonephritis. However, rarely, a tubulointerstitial injury could be present. In the literature review, eighteen cases of simultaneous diagnosis of AAV and IgG4-related disease (IgG4-RD) were described, raising the possibility of an overlap syndrome. We report a case of crescentic pauci-immune glomerulonephritis associated with a dense lymphoplasmacytic infiltrate of IgG4+ plasma cells.

An 83-year-old woman, with a history of pulmonary tuberculosis and hypertension, was hospitalized with diarrhea, vomiting and renal failure. Five months before admission, the patient presented with anorexia, weight loss and fatigue. At this time, she was treated with iron supplementation for normocytic hypochromic anemia (hemoglobin – Hb – of 9.5 g/dL) and blood tests showed serum creatinine(sCr) of 1.5 mg/dL (previous sCr 0.89 mg/dL).

At the hospital admission, initial examination was unremarkable, except for signs of dehydration. Blood tests revealed sCr of 4.2 mg/dL, metabolic acidosis with acidemia, hyperkalemia and anemia (Hb 7.8 g/dL). C-reactive protein and sedimentation rate were elevated and serum albumin was decreased (2.9 g/dL). Urine exam had a protein-creatinine ratio of 2.1 g/g crea, erythrocyturia and leukocyturia. Renal ultrasound was normal. After intravenous fluids and hypokalemic measures, the kidney function stabilized on sCr of 3.5 mg/dL. Further investigation revealed elevated serum IgG (1714 mg/dL) and serum myeloperoxidase-ANCA [66 (<20 U/Q)]. Proteinase 3-ANCA and anti-glomerular basement membrane antibodies were negative. On light microscopy kidney biopsy showed a severe interstitial lymphoplasmacytic infiltrate and cellular crescentic lesions (4/8) – Fig. 1. There were no signs of storiform pattern of fibrosis or obliterative phlebitis. The immunofluorescence revealed granular deposits for C3 (++) on tubules, Bowman capsule and glomerular mesangium. The immunohistochemical study revealed >30 IgG4 positive plasmocytes per large magnification field. Assuming AAV, the patient started methylprednisolone for three days (500 mg/day) and then 1 mg/kg/day of oral prednisolone. The diagnosis of microscopic polyangiitis was made according to the EUVAS classification criteria. Further results of subclasses of IgG revealed IgG1 elevated and normal IgG2, IgG3 and IgG4. Given the severity of the disease, the patient was proposed to Rituximab (375 mg/m^2). After 2-weeks of treatment, the patient showed improvement of kidney function (sCr 2.8 mg/dL) and reduction of proteinuria (<1 g/day). In the three-months following rituximab, the patient had several infectious complications (urinary, pulmonary, CMV with hepatic involvement), with increasing severity and requiring prolonged hospitalization. Unfortunately, in the last hospitalization, she had a cardiorespiratory arrest and died.

The AAV is characterized by inflammation and destruction of small- and medium-sized blood vessels and the presence of circulating ANCA.[1] Although the glomerulus is the most affected, it is common to see tubulointerstitial injury, especially if there is a rupture of Bowman's capsule. In rare cases, the tubulointerstitial involvement is extensive and not associated with glomerular damage. A recent study described the degree of plasma cell infiltrate in AAV and 2/3 of the cases had at least 15% of plasma cell infiltrate and some had over 45%.[2] Neutrophils and ANCA are the main mediators of vessel injury, but plasma cells seem to have a role in AAV-GN, although not clearly understood.[1] It was proposed that B-cells producing ANCA autoantibodies are selected in an inflamed microenvironment and mature to pathogenic plasma cells producing proinflammatory ANCA.[3] This role in local inflammation might be the early acute lesion in AAV-GN.[2,4] Moreover, serum IgG4 elevation has also been associated to active AAV and was proposed as a biomarker of AAV activity.[5]

IgG4-RD, on the other hand, is a lymphoproliferative disease characterized by the infiltration of IgG4-positive plasma cells and elevation of serum IgG4/IgG levels. A dense lymphoplasmacytic infiltrate is the hallmark, but the specificity of this lesion remains controversial. The storiform pattern of fibrosis and obliterative phlebitis are more specific lesions and the presence of two of these three major features are required for a more confident diagnosis.[6]

Although our patient had histologic features and serologic criteria of IgG4-RD, we do not believe that there is an overlap of AAV and IgG4-RD. Plasma cells and IgG4 seem to have a

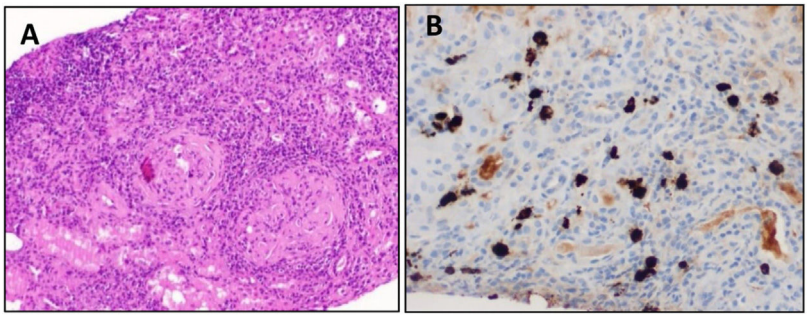

Fig. 1 – Renal biopsy specimen. (A) Light microscopy shows a severe interstitial lymphoplasmacytic infiltrate (H&E, 20×). (B) The immunohistochemical study revels > 30 IgG4 positive plasmocytes per large magnification field (IgG 4 immunohistochemistry, 40×).

more important role in AAV pathogenesis that we though previously. We would like to highlight the importance of a careful examination to distinguish between IgG4-RD and tubulointerstitial nephritis caused by AAV, and not overdiagnose IgG4-RD. The differential diagnosis of these entities it is crucial in terms of treatment and prognosis, since AAV require a more aggressive immunosuppression, given its severity, and presents a worse outcome, particularly with renal involvement.

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https://doi.org/10.1016/j.nefroe.2022.11.020