Case report - IgA nephropathy ANCA positive with favorable outcome

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Abstract

Introduction: The antineutrophil cytoplasmatic antibody (ANCA) is usually associated with pauci-immune crescentic glomerulonephritis (CrGN). However, the literature show an incidence unexpected high of ANCA in immunocomplex CrNP. The crescent IgA nephropaty is one of CrGN that associated with ANCA **Objective:** To relate an IgA nephropaty ANCA positive and sign of worse prognosis that improved with immunossupression. **Method:** 38-year-old pacient with arterial hypertension, renal impairment (CKD-EPI 37 ml/min/1,73 m^2), non-nephrotic proteinuria and hematuria. He related occasionally epistaxis, rhnosinusitis and one arthritis episode that spontaneously resolved. During de investigation, the ANCA titles were 1/160 and anti-RP3 was positive, however renal biopsy showed IgA nephropaty with 38% of crescents. Regarding IgA nephropaty ANCA positive as the main diagnosis, immunossupression therapy with corticoids (1g IV methilprednisone for 3 days followed by 1 mg/kg/day prednisone) for 6 months and cyclophosphamide (500 mg initially then raise the dose until reach 750 m^2. The patient improved renal function and reduced the proteinuria and ANCA titulation. **Conclusion:** The role of the association between IgA nephropathy and ANCA is it aggressive manifestation characterized by the presence of crescents, tubular atrophy and renal dysfunction, which may regress with early onset of immunosuppression treatment.

Keywords: antibodies, antineutrophil cytoplasmic; glomerulonephritis, IgA; immunoglobulin a; renal insufficiency.

Submitted on: 10/22/2014.
Approved on: 12/04/2014.

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DOI: 10.5935/0101-2800.20150063

Introduction

Antineutrophil cytoplasmic antibodies (ANCA) have been correlated with pauci-immune necrotizing and crescentic glomerulonephritis (PNCGN), a condition of rapid, aggressive progression.[1] Perinuclear ANCA (p-ANCA) and cytoplasmic ANCA (c-ANCA) immunofluorescence (IF) staining patterns identify the presence of myeloperoxidase (MPO) and proteinase 3 (PR3) antibodies, respectively. MPO and PR3 are detected with ELISA assays. In addition to this classic manifestation, the role of ANCA has been studied in individuals diagnosed with immune complex-mediated glomerulonephritis,[2] one example being the case if patients with overlapping findings of crescentic immunoglobulin-A nephropathy (IgAN) and ANCA.[3-6] The incidence of this finding in a retrospective series including 2,250 native renal biopsies was 0.2%.[3] This paper describes the case of an ANCA-positive patient diagnosed with IgAN successfully treated with immunosuppressants.

Case report

A 38-year-old male individual came to the hospital complaining of persistent fever lasting 30 days, respiration-dependent chest pain, coughing, foamy urine, and high blood pressure (150/92 mmHg). He denied he had sputum, hemoptysis, dyspnea, lower limb edema, or

other urinary symptoms. The reported medical history events included episodes allergic rhinitis ten years earlier, nasal ulcers with recurring epistaxis one year earlier, and left-knee joint pain with interphalangeal joint involvement. On admission, the patient had a hemoglobin (Hb) level of 13.1 g/dL, and his creatinine (Cr) was at 2.2 mg/dL. Routine urine tests revealed a pH of 5.0; Hb 3+; Protein: 1+; white blood cell count of 8,000 (normal < 10,000); red blood cell count at 152,000 (normal < 8,000). With these findings in hand, other tests were ordered: 24-hour urinary protein (1044 mg/24h); erythrocyte sedimentation rate (53 mm/H); complement testing (C4-20 mg/dL, C3-140 mg/dL); serologic tests for hepatitis B, hepatitis C, and HIV; and non-reagent rheumatic disease tests (ANA, anti-SM, anti-DNA, and anticardiolipin antibodies). The patient was positive for ANCA (1/160) in IF testing and anti-PR3 positive in the ELISA test. Computerized tomography (CT) scans of the sinuses of the face indicated the patient had inflammatory sinus disease, rhinitis, mucosal thickening in the maxillary sinuses, and a septal spur to the left. Chest CT scans were normal. Abdominal imaging revealed normal kidneys and fatty liver disease.

The patient underwent a renal biopsy procedure. The findings included 13 glomeruli, two with global sclerosis, five with segmental glomerulosclerosis in their capillaries, remnants of cell proliferation, synechiae in the Bowman's capsule, and fibrocellular crescents. The remaining glomeruli had unaltered cell counts and evenly contoured peripheral capillary loops. The tubules had irregular foci of atrophy surrounded by mild interstitial fibrosis. Arteries were within normal range. IF showed diffusely distributed granular deposits in the mesangium extending to the IgA capillary loops (+/2+), C 3 (+), traces of IgM, kappa (+) and lambda chains (+/++).

With these signs in mind, the pathologist diagnosed the patient with IgAN with a pattern of endocapillary proliferative glomerulonephritis (GN) with crescent formation (5/13), global glomerulosclerosis (2/13) and segmental tubular atrophy with mild interstitial fibrosis. The patient had IgAN with crescents in 38% of the biopsy specimen, an Oxford score of M0, E1, S1, T1; he was positive for ANCA and anti-PR3, and negative for infections; therefore, he was started on antiproteinuric drugs, pulse methylprednisolone therapy (1 g/3 days followed by prednisone 1 mg/kg/day), and cyclophosphamide (500 mg with dosage increased to 750 mg/m^2 with an accumulated dose of 5 g/6 months) as he was suspected for ANCA-associated IgAN.

The nasal ulcers disappeared and the patient improved gradually from systemic symptoms; creatinine levels decreased (Cr -1.1), along with proteinuria (550 mg/24h) and ANCA level (1/160, 1/80, 1/40). The side effects of immunosuppression included type-1 *diabetes mellitus* and prednisone dosage was reduced to 40 mg/day.

Despite the classical association between PNCGN and ANCA, 25% of the cases of immune complex PNCGN are ANCA-positive.[2] The patient described in this case had systemic symptoms, nasal ulcers, nephritic syndrome, and positive ANCA and anti-PR3 tests, but renal biopsy findings consistent with IgAN in 38% of the specimen.

IgAN is characterized by the presence of IgA deposits in the mesangium and codominant deposits of IgM, IgG, and C3.[7] Crescentic disease is defined by the presence of more than 50% of crescents in the biopsy specimen and is a sign of poorer prognosis. Studies have shown that immunosuppressants are not always effective in resolving inflammatory injuries, which mostly progress to interstitial fibrosis and glomerulosclerosis.[8,9] The histology findings related to poorer prognosis in IgAN are mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), and tubular atrophy/interstitial fibrosis (T).[7] The M, S and T scores have been correlated with proteinuria, hypertension and kidney disorders at the time of biopsy, in addition to predicting renal outcome independently from clinical variables. Evidence indicates that score E identifies better

response to immunosuppression.[10,11] Clinical findings of kidney disease, proteinuria, and hypertension and the time of diagnosis have also been associated with poorer prognosis.

Haas *et al.*[3] carried out a study to establish the histology criteria to differentiate between the ANCA-positive and ANCA-negative forms of crescentic IgAN. Six biopsy specimens with ANCA-positive, anti-MP3 and/or anti-PR3-positive crescentic IgAN were compared to eight biopsy specimens with classical disease. Crescents were found in 50% of the surface of the six specimens with ANCA-positive disease, along with diffuse mesangial deposits with at least 1+ (scale 0-4+) of IgA on IF without involvement of glomerular capillary loops confirmed by scanning electron microscopy. Codominant deposits of C3, IgM, and/or IgG were present, but IgA was predominantly found in every case. The ANCA-positive group had very little mesangial and endocapillary hypercellularity.

Bantis *et al.*[4] also looked into the histology patterns and response to therapy of the two injury types. The authors assessed patients with more than 10% of crescents in their renal biopsies from a series of 339 cases of IgAN. ANCA-positive patients (n = 8) had mesangial IgA deposits 1-2+ (1+,50%; 2+,50%), greater percentages of crescents, greater degrees of tubular atrophy, lower glomerular cellularity rates, and absence of IgA deposits in the capillary loops. ANCA-negative controls (n = 26) had a similar pattern in terms of mesangial deposits (+,52%; 2+,40%; 3+,8%), higher degrees of mesangial hypercellularity; 42% had deposits in the glomerular capillaries.[4] These deposits may be present in a third of the cases of IgAN.[10] They have been correlated with active disease indicated by mesangial and endocapillary hypercellularity, and some authors have associated them with the presence of crescents in the biopsy specimen.[10] Nonetheless, the ANCA-positive group, characterized by absence of deposits, had a higher percentage of crescents. The study also found better response to immunosuppressant therapy in the ANCA-positive group.[4] The clinical manifestations seen in ANCA-positive patients with IgAN reported in both studies were asthenia, hemoptysis, joint pain, and kidney failure.[3,4]

Examination on a light microscope and IF testing revealed the patient described in this case report had more than 10% of crescents in his renal biopsy specimen, a sign associated with poor prognosis in the literature. Consequently, he was started on immunosuppressants.

The clinical presentation, histology patterns, and response to immunosuppressant therapy observed in this patient with ANCA-associated IgAN were similar to previous reports published in the literature. Pulse methylprednisolone therapy converted to monthly prednisone and cyclophosphamide resulted in improved renal function, decreased urine protein, and lower ANCA levels. The pathophysiological mechanisms involved in the occurrence of ANCA-associated IgAN have not been established. The disease could stem from a random association of vasculitis and incipient IgAN. However, according to some authors ANCA works in synergy with immune complexes to trigger PNCGN, while the inflammatory state inherent to IgAN supports the appearance of ANCA and consequently increases glomerular damage.[3] More studies are required to clarify the actual role of ANCA in immune complex glomerulonephritis.

The importance of identifying this pattern of overlapping diseases lies in the aggressiveness of ANCA-associated IgAN, defined by the presence of crescents, tubular atrophy, and renal involvement, which may regress with early administration of immunosuppressants. In this context, the inclusion of tests for ANCA in clinical practice - IF and ELISA - for crescentic and necrotizing disease has been recommended in the literature.[3]

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