Immune-complex deposits in "pauci-immune" glomerulonephritis: a case report and brief review of recent literature

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Abstract

Anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis is considered a "pauci-immune" disease, characterized by absent or mild glomerular tuft staining for immunoglobulin and/or complement. We describe a 72-year-old man with progressive renal failure over five months who was found to have P-ANCA associated crescentic glomerulonephritis. Renal biopsy also revealed immunofluorescence staining for Immunoglobulin G and C3. Treatment comprised corticosteroids, cyclophosphamide, and plasmapheresis but unfortunately kidney function did not recover, likely due to substantial interstitial fibrosis at diagnosis. This case illustrates that serologic evaluation for ANCAs should not be discounted when immune deposits are present. Prompt diagnosis is warranted.

Key words: anti-neutrophil cytoplasmic antibodies, glomerulonephritis, immune deposits.

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis is associated with rapidly declining renal function, and often leads to end-stage renal disease (ESRD) or death if not treated promptly and aggressively [1]. The disease is typically characterized by "pauci-immune" cresentic glomerulonephritis. However, there are a few reports of ANCA-associated glomerulonephritis with immune deposits in the literature, and the exact role of these deposits is not well understood [2-4].

Case report

A 72-year-old man with hypertension and chronic obstructive pulmonary disease was referred to our institution for evaluation and management of renal failure. He had been followed at an outside facility with progressively deteriorating renal function over several months. Serum creatinine was 1.6 mg/dl 5 months previously, and rose to 3.8 mg/dl in the next 3 months. Initially, renal insufficiency was attributed to prostatic outlet obstruction. However, renal function did not improve with attempts to relieve obstruction by prostatectomy. Nephrotic-range proteinuria was also detected at 3.6 g of urinary protein per day. On presentation to our institution, physical

examination demonstrated blood pressure 190/105 mmHg, bibasilar rales, and bilateral lower extremity pitting edema. Initial pertinent laboratory results included blood urea nitrogen (BUN) 50 mg/dl, creatinine 7.2 mg/dl, positive ANCA by immunofluorescense (IF) of perinuclear or P-ANCA pattern and titer of 1 : 80. Myeloperoxidase antibody was positive but serine protease 3 antibody was negative. Urinalysis showed microscopic hematuria. Renal biopsy revealed active necrotizing crescentic glomerulonephritis with focal segmental glomerulosclerosis, extensive tubular atrophy and interstitial fibrosis (Figure 1A). Immunofluorescence demonstrated 2-3 + IgG immunoglobulin (Figure 1B) and C3 complement staining of the capillary walls (Figure 1C). The patient was placed on hemodialysis for management of volume overload and azotemia. Given the active component of necrosis and positive serum P-ANCA, he also received ten sessions of plasmapheresis, cyclophosphamide 100 mg daily, and methylprednisone 1 mg intravenously daily for three days followed by oral prednisone 1 mg/kg daily. Cyclophosphamide was reduced to 75 mg daily after 3 months and stopped at month 6. Prednisone was tapered to 15 mg daily by month three, then to 7.5 mg daily by month 6, and finally reduced by 1 mg daily every 3 to 4 weeks to discontinuation. The patient tolerated the treatment without complications, but remained hemodialysis-dependant over the year of follow-up.

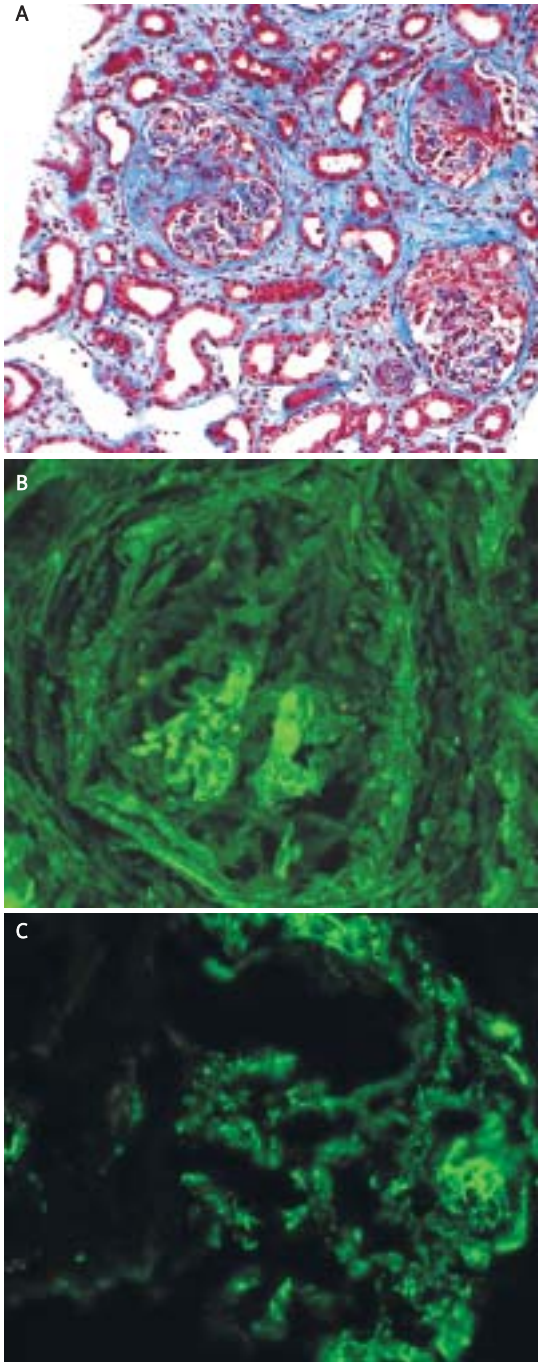

Figure 1. Biopsy specimen in the current case. (A) Light microscopy showing active necrotizing and crescentic glomerulonephritis, secondary focal and segmental glomerulosclerosis, and extensive tubular atrophy and interstitial fibrosis. (B) Immunofluorescence for IgG demonstrating granular 2+ staining along capillary walls. (C) Immunofluorescence for C3 showing granular 2-3+ deposits along capillary walls

Discussion

Anti-neutrophil cytoplasmic antibody was first reported in 1982 by Davies *et al.* [5] in patients with segmental necrotizing glomerulonephritis on biopsy and absent or scant, irregular deposits by direct immunoflorescence. The word "pauci" is derived from Latin which means few, and the observation of cresecentic glomerulonephritis with a paucity of IF staining for immunoglobulins led to the original definition of pauci-immune glomerulonephritis. Anti-neutrophil cytoplasmic antibody has since been described as a characteristic serological marker of small vessel vasculitides, including Wegener's granulomatosis, microscopic polyangitis, Churg-Strauss syndrome and renal-limited vasculitis [6-8].

The pathophysiology underlying ANCA-associated crescentic glomerulonephritis classically entails the presence of auto-antibodies directed against certain cytoplasmic components of circulating neutrophils (myeloperoxidase or serine protease 3 antibodies) [9, 10]. In the glomerular tuft, antibody binding at the endothelium leads to neutrophil activation, necrotizing injury and inflammation; this also may occur in other tiny vascular beds in the body. Active inflammation is often followed by the development of fibro-cellular and fibrous crescents.

The clinical course of ANCA-associated glomerulonephritis is characterized by insidious onset of hematuria and renal insufficiency. Systemic involvement can occur and usually involves the skin, lungs, musculoskeletal, and nervous systems. Rapid decline in renal function is common, and delay in diagnosis and treatment is associated with high risk of ESRD or even death [1]. Prior to the introduction of

immunosuppressive treatments, median survival with pauci-immune vasculitis was 5 months [11], but survival steadily improved with the introduction of immunosuppressive agents. In the early 1970s, Fauci *et al*. [12] introduced cyclophosphamide in combination with corticosteroids as an effective treatment for pauci-immune vasculitis and observed a complete remission rate of 75%. Recent studies suggest that azathioprine may be as effective as cyclophosphamide in inducing remission of ANCA-medicated vasculitis [13, 14]. However, the prognosis for patients with significant renal injury is distinctly poor. Plasmapheresis has been increasingly adopted as adjunctive therapy for rapidly progressive ANCA-associated glomerulonephritis [15]. A recent randomized controlled trial confirmed the efficacy of plasma exchange, demonstrating a 24% absolute reduction in the risk of progression to ESRD at 12 months, from 43% to 19%, compared to intravenous methylprednisolone (in addition to cyclophosphamide and prednisone for all patients) [16]. In our case, plasmapheresis was attempted along with immunosuppressive agents based on the presence of active necrotizing crescents on renal biopsy findings, and the patient tolerated the therapy without major adverse events. Unfortunately, he remained dialysis-dependent, likely because the process had progressed to yield substantial interstitial fibrosis by the time of diagnosis and treatment.

Although ANCA-associated glomerulonephritis is classically pauci-immune, our case demonstrated IF

Table I. Summary of published cases of "pauci-immune" glomerulonephritis with immune deposits and clinical outcomes

Author	Cases (*n*)	Cases with positive IF (Ig), and degree of positivity	Management	Outcomes data (IF positive vs. negative)
Neumann *et al.* [4]	37	6 (IgM, IgA), 1 (IgG, C3), ≥ 2+	CP, P	Ig deposition associated with more proteinuria (5.4 ±3.1 vs. 1.3 ±1.0 g/24 h; $p = 0.016$) and a non-significant trend towards worse renal survival
Lanham *et al.* [17]	5	4 (Ig M, C3), 1 (IgA)	P and/or CP, AZT	Rapid initial response in all cases. Only one case developed significant renal failure that was successfully reversed with treatment
Vrtovsnik *et al.* [18]	1	1 (IgA)	Pulse CP, P	NR
Andrassy *et al.* [19]	25	2 (IgA), "mild-to-moderate" deposits	P for 9 months after clinical remission and CP (with uromitexan) for 2 years after remission, followed by either AZT or termination of treatment	NR
Brouwer *et al.* [20]	20	7 (IgM) 10 (C3)	NR	NR
Grotz *et al.* [21]	1	10 (C3, IgM, IgG, or IgA)	CP, P (13 patients) and plasma exchange (9 patients)	NR
Ronco *et al.* [22]	41	3 (IgG, IgM), 2 (IgA), 12 (C3); "significant" deposits	P, CP (20 patients), P (29 patients), AZT (2 patients), plasmapheresis (2 patients)	NR
Hu *et al.* [23]	2	2 (IgG, IgA, IgM, and/or C3)	P	NR
Pinching *et al.* [24]	13	8 (IgG), 5 (IgM), 12 (C3)	P, CP and/or plasma-pheresis for initial control of fulminant cases	Reversal of renal failure with combination therapy
Haas *et al.* [2]	126	68 (IgM, IgG, IgA, C3 and/or C1q)	CP and corticosteroid	Ig deposition associated with higher median proteinuria (3.2 vs. 1.3 g/24 h, $p < 0.0001$), and a non-significant trend towards higher serum creatinine

CP – cyclophosphamide, P – predinisolone, AZT – azathioprine, IF – immunofluorescence, Ig – immunoglobulin, NR – not reported

staining for IgG and C3 deposits. We searched the MEDLINE/PubMed electronic database for publications on ANCA-associated glomerulonephritis with IF staining published in English language from 1983 to 2009 using the MeSH terms "ANCA", "glomerulonephritis", and "immune deposits". The search yielded ten relevant articles that comprised case reports and small case series (Table I). Among 281 biopsies that were described in patients with ANCA-associated glomerulonephritis, 154 biopsies (54%) showed positive IF for IgG, IgM, IgA, and/or complements. The proportion of biopsies with heavy staining could not be ascertained as the degree of positivity was not reported for all cases. In general, the patients were treated with corticosteroids and cyclophosphamide, and some received plasmapheresis. The majority of the cases showed good response to these regimens. Neumann *et al.* [4] and Haas and Eustace [2] observed significantly heavier proteinuria and trends towards worse renal function in the subsets with immune deposits.

The pathophysiologic role of immune deposits in patients with ANCA-mediated vasculitis is unclear. The hypothesis that immune complexes act synergistically with ANCA to produce more severe glomerulonephritis, as manifest by heavier proteinuria and inferior kidney function, was raised by some authors [2, 4]. There are also reports of predominant mesangial IgA deposits described as concomitant ANCA-associated glomerulonephritis and IgA nephropathy [3, 18]. Findings from several animal studies have lead to the notion that early immune complex deposition may play a role in the initiation of vasculitis and glomerulonephritis [25, 26]. A transient immune deposit was observed in an animal model of ANCA-associated glomerulonephritis following injection of rats with myeloperoxidase [25]. In some models, it was postulated that immune complex deposits disappeared before tissue biopsy was performed.

In conclusion, immune deposits may be found in a subset of patients with ANCA-associated glomerulonephritis. Anti-neutrophil cytoplasmic antibody-associated glomerulonephritis is an aggressive disease that warrants prompt diagnosis and treatment. It is important to test for serological markers such as ANCA even in cases with active IF and immune deposits on renal histology. Cases such as ours also raise the question of whether ANCA-associated glomerulonephritis is truly pauci-immune. Perhaps, deposits that appear early in the disease process are commonly degraded, or the observation may represent an overlap of two disease forms. Additional studies are warranted to further understand the definitive role and best treatment of patients with ANCA-associated glomerulonephritis and immune deposits.

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