Renal Limited Pauci-Immune Vasculitis: A Case Report And Review Of Literature

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Abstracts

Antineutrophil cytoplasmic antibody (ANCA) associated vasculitis limited to the kidney is characterized by necrotizing glomerulonephritis with little or no deposition of immuno-reactants (IgG, IgM, IgA, and complement components). We present here a case with renal limited vasculitis and discuss the literature.

Key Words: Vasculitis, Renal Limited, Antineutrophil cytolplasmic antibodies, crescents.

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INTRODUCTION:

Antineutrophil cytoplasmic antibody (ANCA) associated vasculitis limited to the kidney is characterized by necrotizing glomerulonephritis with little or no deposition of immuno-reactants (IgG, IgM, IgA, and complement components). Extra renal manifestations, by definition are not seen, at least at presentation. The course of the disease may be severe leading to renal failure in a sizeable population.

We present a case of renal limited ANCA associated vasculitis with subsequent review of literature.

CASE REPORT

A 28 years old male was admitted under department of nephrology at our hospital with complaints of bilateral pedal edema for the past 2 months. On review of systems, it was revealed that he had one episode of bilateral red eyes about 8 months ago which was not accompanied by visual problems. He also had joints aches and pains about 7 months ago which were not accompanied by early morning stiffness, joint swelling, rash, photophobia,

oral or genital ulcers or hair loss. There was a history of skin rash about 3 months before presentation which was treated as furunculosis with skin ointments and antibiotics. This rash resolved and never recurred. About 2 months ago he started noticing pedal edema and periorbital puffiness. He did not notice shortness of breath, orthopnea, cough, fever, chest or abdominal pain, dysuria, hematuria, loin pain, epistaxis, ear discharge, hearing loss or paresthesia. There were on and off headaches, loss of taste and generalized weakness.

The patient was a car mechanic in the gulf country and was evaluated eye and joint symptoms and a serology for Brucellosis was negative. He returned to Pakistan and obtained a rheumatology consultation 3 months prior to presentation. The musculoskeletal systems examination was normal and he was advised to obtain a dermatology consultation for the skin rash. A urine exam was not done however serum creatinine was 1.66 mg/dL. He was also asked to obtain a nephrology consult.

By virtue of his job, he was frequently exposed to petroleum and petroleum based products. He also admitted to have used herbal medications as well as over the counter analgesics. He denied use of illicit drugs or alcohol or being sexually promiscuous.

TABLE 1: Laboratory investigations of patient with pauci immune vasculitis with follow up.

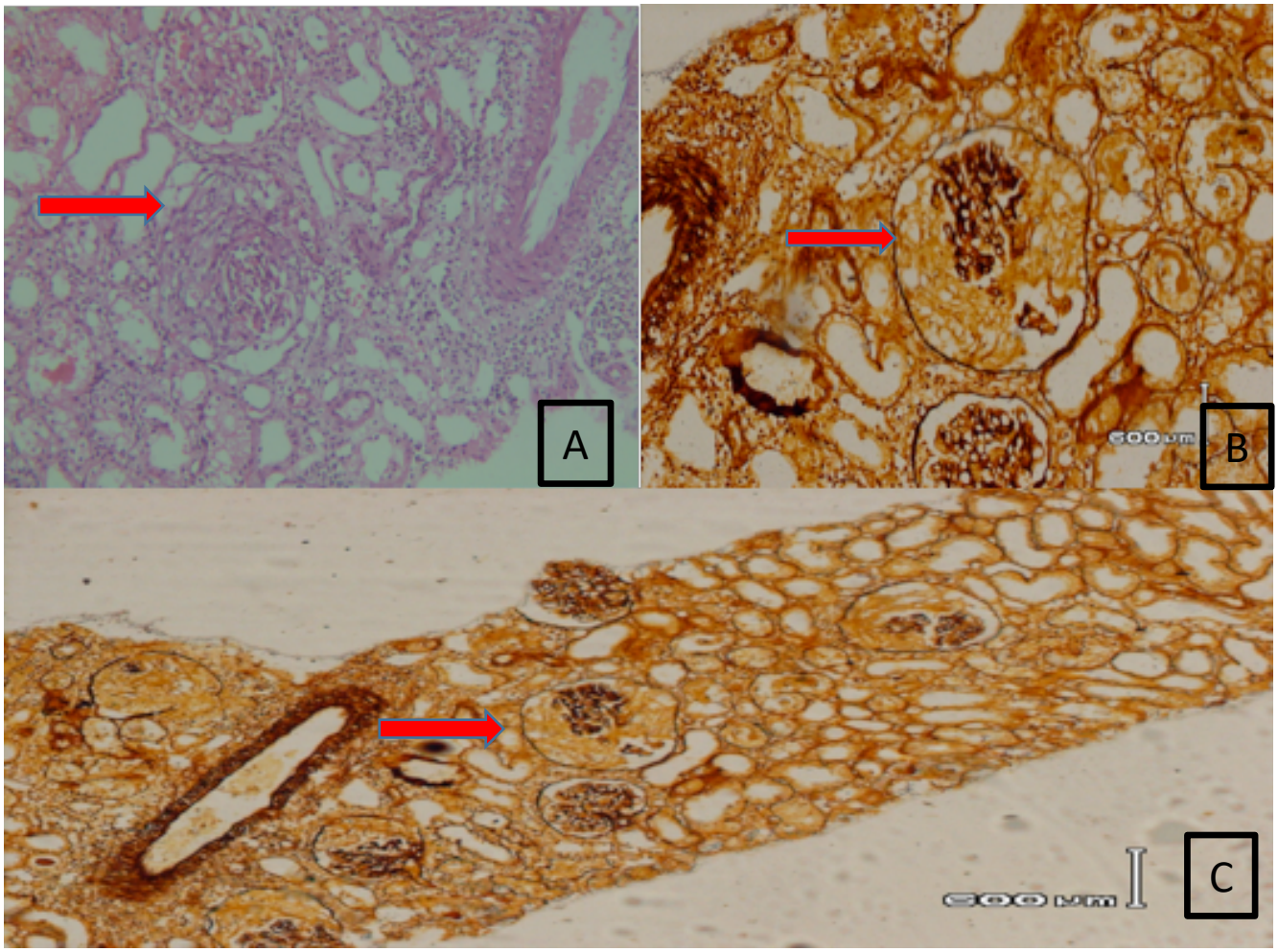
PARAMETER	May 25 2013	October 8 2013	October 13 2013	October 26, 2013	June 2015	December 2017
WBC Count ($/mm^3$)	7900	7760	7690	6520		
PMN (%)	60	64	65	75		
LYMPHO. (%)	33	33	31	21		
Platelet ($/mm^3$)	469000	643000	569000			
Urine Complete Exam		Proteins ++ RBCs: MANY Casts: Neg.	Proteins ++ RBCs: 5 - 10		Proteins NIL RBCs NIL	Proteins NIlL RBCs NIL
Serum Creatinine (mg/dL)		1.66	1.37	1.21	1 mg/dL	0.9 mg/dL
CRP		67.9				
ANA		Negative				
RA FACTOR		Negative				
ENA		Negative				
ANTI CCP		Negative				
ANTI HCV		Non- reactive				
HBsAg		Non- reactive				
ANTI HIV 1, 2	Negative					
VDRL	Negative					
C3		Normal				
C4		Normal				
X Ray Chest	Normal					

Examination revealed a well-built male with a blood pressure of 110/70 mmHg, heart rate of 78/minute, adequate urine output and pedal edema bilaterally. Rest of the systemic examination was normal.

His investigations are shown in table (Table 1).

On the basis of these investigations renal biopsy was planned. Histo-pathological and immunostaining examination showed the presence of epithelial crescents and pauci-immune glomerulonephritis (Figure 1 and 2).

FIG 1: Histopathology slides: **Panel A:** H&E staining showing a cellular crescent marked by arrows. **Panel B and C:** John Methanamine Silver Stain showing crescents in majority of the glomeruli.



A diagnosis of Renal Limited Pauci Immune Glomerulonephritis causing rapidly progressive glomerulonephritis was made and the patient was given methylprednisolone intravenously at a dose of 500 mg/d IV for three days, afterwards prednisolone was started at 60 mg/d.

Cyclophosphamide pulse was given intravenous 500 mg with plan for repeat pulses at monthly intervals.

As the suspicion of pauci-immune glomerulonephritis was strong, ANCA serology was requested which showed strongly positive C-ANCA (32 IU/L, Range: 1 – 6 IU/L).

After receiving six doses of cyclophosphamide the patient was placed on oral Azathioprine, which was continued for a period of 18 months (till June 2015) by which time, he had achieved complete remission. He is still abroad for his job. At the last follow up in December 2017, the urine examination was bland. Serum Creatinine was stable at 0.8 mg/dL.

DISCUSSION:

ANCA associated vasculitis is a disorder involving small vessels. This is a spectrum of diseases that include Wegener's Granulomatosis (WG; 90% positive for C ANCA), Microscopic Polyangiitis (MPA; 70% positive for p-ANCA, 25% positive for c-ANCA), Churg Strauss Syndrome (CSS; 50% patients positive for c-ANCA), Renal Limited (Pauci-Immune) Vasculitis (35% positive for c-ANCA, 45 % positive for p-ANCA) and Drug Induced (ANCA Associated) Vasculitis (caused by exposure to Propylthiouracil, Hydralazine and Minocycline).[1]

The diagnosis is based upon characteristic history of organ involvement. In contrast to systemic ANCA associated vasculitis i.e. WG, CSS and MPA the patients with renal limited vasculitis do not have evidence of extra renal disease. Our patient had renal limited form of ANCA associated small vessel vasculitis (AASVV), extensive search at the time of diagnosis did not reveal any other organ system involvement. These patients may rarely develop extra renal manifestations and evolve into other classic forms of small vessel vasculitis i.e. Wegener's Granulomatosis or Microscopic Polyangiitis.[2]. The follow up of this patient over the next three years also did not reveal any extra-renal manifestation.

Laboratory investigations may reveal non-specific abnormalities like raised CRP as seen in our patient. Urine examination may be significant for the presence of red cell casts however our patient's urine examination only revealed the presence of red blood cells and protein. The serological tests including ANA, Anti CCP and ENA are usually negative as seen in our patient. However presence of PR3 ANCA is seen in up to 35% of the cases.[1] This antibody was highly positive in our patient.

The histopathology on kidney biopsy in these patients can be described as sclerotic, crescentic, focal and mixed[3]. Our patients kidney biopsy revealed the presence of epithelial crescents in more than 50% of the glomeruli thus classifying it as crescentic glomerulonephritis. Immunofluorescence is typically negative for deposition of immunoglobulin and complement thus giving it the name of pauci immune glomerulonephritis. Immunostaining was carried out in our patient and it was negative.

The treatment of renal limited form of ANCA associated glomerulonephritis does not differ much from treatment of the generalized disease. The treatment involves the use of steroids, immunosuppressive agents or, more recently, monoclonal antibodies. The treatment regimen consists of two phases: Induction and Maintenance Phase. Combination therapy with oral cyclophosphamide and prednisolone has been used for remission induction of ANCA-associated vasculitis since the 1970s.[4] However it is felt that pulsed cyclophosphamide is more likely to result in remission than continuous oral therapy, and with a lower risk of side effects although pulsed therapy may be associated with a higher risk of relapse.[5] This role of pulsed therapy was confirmed by the European Vasculitis Study (EUVAS) investigators as well.[6] We decided to use pulsed cyclophosphamide therapy at monthly intervals (total of six

pulses) along with tapering doses of steroids as the patient was unable to obtain oral cyclophosphamide at his place of work. Plasma exchange was not considered as the baseline creatinine was only 1.6 mg/dl, had it been higher we would have advised plasma exchange as a part of remission induction.[7]

After remission is achieved there is evidence to believe that azathioprine may be as effective and safer than cyclophosphamide in maintaining remission.[8,9] It is available easily and is cheap making it an automatic choice for our patient who belongs to a financially challenged background. Methotrexate and leflunomide are other choices however these medications may have more severe side effects as compared to azathioprine.[10] Our patient continued to be on azathioprine for the recommended duration of treatment i.e. 18 months. He is working in Saudi Arabia and on regular follow up with us.

Conclusions:

ANCA associated vasculitis may present in renal limited form. The clinical picture may not always correlate with histopathological findings. The standard of care in these patients is remission induction and maintenance as per regimens described for more generalized disorders.

Conflict of Interest

None

References

1. Weidner S, Geuss S, Hafezi-Rachti S, Wonka A, Rupprecht H. ANCA-associated vasculitis with renal involvement: an outcome analysis. Nephrol Dial Transplant. 2004; 19: 1403–11

2. Woodworth TG, Abuelo JG, Austin HA III, Espara A. Severe glomerulonephritis with late emergence of classic Wegener's granulomatosis. Report of 4 cases and review of the literature. Medicine (Baltimore) 1987; 66:181

3. Berden AE, Ferrario F, Hagen EC, Jayne DR, Jennette JC, Joh K. Histopathologic Classification of ANCA-Associated Glomerulonephritis. J Am Soc Nephrol. 2010; 21: 1628–36.

4. Hoffman GS, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, Travis WD, et al. Wegener granulomatosis: an analysis of 158 patients. Ann Intern Med. 1992;116:488–98.

5. de Groot K, Schmidt DK, Arlt AC, Gross WL, Reinhold-Keller E, Wolfgang L. Standardized neurologic evaluations of 128 patients with Wegener granulomatosis. Arch Neurol 2001;58:1215–21.

6. Adu D, Pall A, Luqmani RA, Richards NT, Howie AJ, Emery P, et al. Controlled trial of pulse versus continuous prednisolone and cyclophosphamide in the treatment of systemic vasculitis. QJM 1997;90:401–9.

7.Guillevin L, Cordier JF, Lhote F, Cohen P, Jarrousse B, Royer I, et al. A prospective, multicenter, randomized trial comparing steroids and pulse cyclophosphamide versus steroids and oral cyclophosphamide in the treatment of generalized Wegener's granulomatosis. Arthritis Rheum 1997;40:2187–98.

8. Jayne DR, Gaskin G, Rasmussen N, Abramowicz D, Ferrario F, Guillevin L, et al. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. J Am Soc Nephrol 2007;18:2180–8.

9. de Joode AAE, Sanders JSF, Puéchal X, Guillevin LP, Hiemstra TF, Flossmann O et al. Long term azathioprine maintenance therapy in ANCA-associated vasculitis: combined results of long-term follow-up data. Rheumatology (Oxford). 2017;56(11):1894-1901.

10. Jayne D, Rasmussen N, Andrassy K, Bacon P, Tervaert JW, Dadoniene J, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. NJM 2003;349:36–44.