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MPO ANCA Positivity in IgA Nephropathy: Imposter or Implication?

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Case Report

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ABSTRACT

Background: IgA nephropathy is the most common primary glomerulonephritis, while the most common cause of rapidly progressive glomerulonephritis (RPGN) is pauci immune crescentic glomerulonephritis (GN), followed by Immune complex mediated GN and anti Glomerular basement membrane (GBM) disease. Anti neutrophil cytoplasmic autoantibody (ANCA) is characterised by crescentic necrotizing GN on renal biopsy with minimal deposits. Immunoglobulin A (IgA) nephropathy may present as crescentic GN with mesangial IgA deposits and sometimes around capillary as well. The co existence of circulating ANCA in a patient of IgA nephropathy with RPGN presentation is a rare phenomenon and very less literature is available for the same.

Case Presentation: This case describes a rare presentation of RPGN which was myeloperoxidase (MPO) positive on enzyme immunoassay (EIA) with central nervous system (CNS) vasculitis presenting as hemiparesis. Patient was treated as ANCA vasculitis, with plasmapheresis (PLEX) and Cyclophosphamide as Standard of care as KDIGO suggests treatment may be initiated without biopsy when presence of RPGN picture with circulating ANCA. However, renal biopsy, later revealed features of crescentic IgA nephropathy but the presence of systemic symptoms makes IgA

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nephropathy as the sole diagnosis highly unlikely, hence a possibility of MPO IgA concurrence remains high. Hence our case was treated in the lines of ANCA vasculitis with IV cyclophosphamide according to EUVAS protocol. Our case is at sustained remission at 6 months after 10 doses of cyclophosphamide as SOC and has now been shifted to maintenance therapy on Azathioprine (Aza), given the possibility of relapse.

Conclusion: Hence MPO ANCA vasculitis and IgA nephropathy is a very rare concurrence. The presence of CNS vasculitis in this background is never reported. However, this case drastically improved with Pulse cyclophosphamide and corticosteroids.

Keywords: MPO vasculitis; IgA nephropathy; crescentic GN; RPGN; biopsy.

ABBREVIATIONS

RPGN : Rapidly Progressive Glomerulonephritis
GN : Glomerulonephritis
GBM : Glomerular Basement Membrane
MPO : Myeloperoxidase
EIA : Enzyme Immunoassay
PLEX : Plasmapheresis
IgA : IMMUNOGLOBULIN A
AAV : ANCA Associated Vasculitis
SOC : Standard of Care
IgAN : Immunoglobulin A Nephropathy

1. INTRODUCTION

Immunoglobulin A (IgA) nephropathy is the most prevalent primary glomerulonephritis (GN) [1]. Antineutrophil cytoplasmic associated vasculitis (AAV) is the most common cause of rapidly progressive crescentic GN [2]. AAV can be of two types according to enzyme immunoassay (EIA): Myeloperoxidase (MPO) or Proteinase 3 (PR3). However, the coexistence of these two entities is rarely reported, if so, the mutual effect on one another's pathogenesis is questionable. No more than 30 cases of such AAV and IgA nephropathy have been reported with just two case series [3,4].

This case reports highlights the presence of overlapping MPO AAV and IgA nephropathy with presence of extra renal systemic manifestation and similar response to therapy as in isolated AAV: hence predominating the clinical picture [5]. In Crescentic IgA nephropathy though the standard of care (SOC) is similar to AAV; responses is poorer than AAV [6].

2. CASE PRESENTATION

2.1 Patient Particulars

A 54year hypothyroid and hypertensive female patient presented with renal dysfunction and dyspnoea for one and half months. There was no associated frothiness of urine, oliguria, haematuria, fever or extra renal manifestation.

2.2 Clinical Findings

On examination, her blood pressure: 180/110 mm of Hg, pedal oedema: ++, pallor: +; Dipstick: protein 2+, Blood: moderate.

2.3 Baseline Investigations Revealed

Hemoglobin 6.7 gm/dL, platelets 2.2 lakh/mm3 and Total count 8,100/mm3. Serum sodium was 134 mmol/L, potassium 4.2 mmol/L, urea 110mg/dL, creatinine 4.1 mg/dL. HBsAg HCV HIV1 &2 were negative. Urine routine examination showed albumin 2+; 2-3 pus cell; Rbc: 20/hpf and 24 hours quantitative urine protein was 957 mg. Ultrasound of abdomen showed normal sized kidneys with slightly raised cortical echogenicity and maintained cortico-medullary differentiation. Echocardiography showed left ventricular ejection fraction of 67% no regional wall motion abnormality, no pulmonary artery hypertension. HRCT thorax shows- mild sub pleural atelectatic changes in anterior basal segment of left lower lobe, minimal left sided pleural effusion.

As she was diagnosed as a case of rapidly progressive GN, auto immune profile was sent to look for the etiology. C3:77 (low)→normalised after 1 week; C4: 24; ANA (hep 2): negative; PR3 levels: normal; MPO: positive (155) Normal Range (0-20).

Therapeutics: She was initiated on Plasma exchange (PLEX) being a case of MPO AAV (Renal limited). However after 4 session of Plex; she developed seizures and hemiparesis. MRI brain: showed diffuse multiple small patch of T2 weighted hyper intensity and diffuse restriction seen in bilateral cerebral hemispheres all the lobes in both grey and white matter, some in right cerebellum: hence a diagnosis of Central

nervous system vasculitis was made. She was then further managed on the lines of systemic AAV with Intravenous Cyclophosphamide.

3. RENAL BIOPSY DONE AT AFTER COMPLETION OF PLEX REVEALED

3.1 Light Microscopy

11 glomeruli identified; 2 are segmentally sclerosed with adhesion formation. Rest 9 non sclerosed tufts show enlargement, diffuse matrix mesangial expansion and mesangial hyper cellularity. Total 6 glomeruli show crescent formation: 4 are circumferential (3 fibro cellular, 1 fibrous) and 2 are segmental (1 fibro cellular, 1 fibrous). GBM fragmented at site of crescent formation. Tubules: mild atrophy. Vessels: arteriolar medial thickening. Interstitium: mild fibrosis. Focal lymphocytic infiltration in scarred interstitium. IF/ TA: 10% (Picture 1).

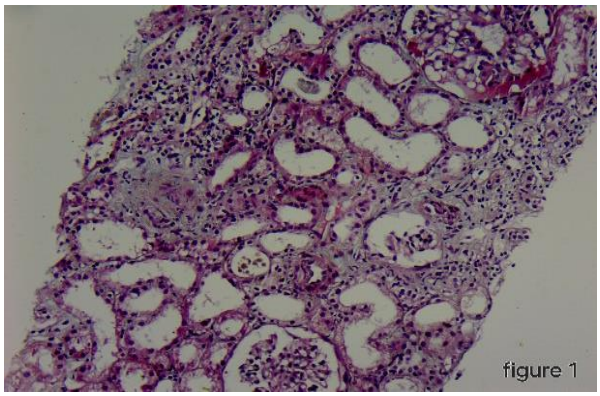
3.2 Immunofluorescence

11 glomeruli:- IgG: negative; IgA: 2+ granular mesangial deposit; IgM: negative; C3c: 1+ granular mesangial deposit; C1q: negative; Kappa: 1+ granular mesangial deposit; Lambda: 2+ granular mesangial deposit (Picture 2).

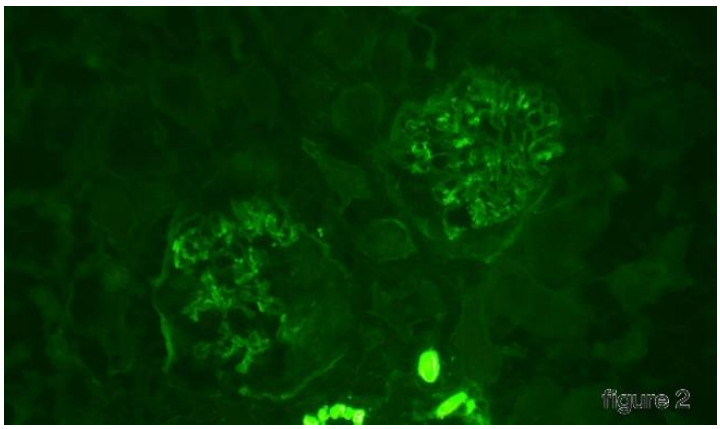
3.3 Impression

Crescentic and sclerosing glomerulonephritis with mild tubulointerstitial chronicity. Considering serology and DIF, possibility of combined IgA nephropathy (M1 E0 S1 T0 C2) with AAV remains strong.

As crescentic IgA is to be managed on the lines of AAV and possibility of MPO IgA nephropathy overlap in background of systemic features, patient completed 10 doses of Cyclophosphamide Intravenous @12.5mg/kg. Her creatinine stabilised to 1.2 after 6 months and was off dialysis since completion of PLEX. Being MPO titre high positive and presence of extra renal symptoms as CNS vasculitis, she was initiated on maintenance therapy with Azathioprine @2mg/kg on the lines of AAV with no further relapse till date in sustained remission for past 6 months.



Picture 1. Focal lymphocytic infiltration in scarred interstitium



Picture 2. Granular mesangial deposit

4. DISCUSSION

AAV is usually diagnosed by EIA with MPO/PR3 antibody levels and confirmed on biopsy by presence of pauci immune necrotizing and crescentic GN on biopsy. Systemic features may be present in MPO AAV [7]. However in cases of rapidly deteriorating renal function, if high titre of MPO/ PR3 AAV is positive, treatment with plasmapheresis may be initiated without confirmation on biopsy [8]. C3 may be low in about 20% of AAV [9].

IgA nephropathy usually presents asymptomatically or with macroscopic hematuria, [10] RPGN as a presenting feature is rare [11]. Presence of systemic features with IgA nephropathy unlikely encountered.

Concurrent presence of MPO high titres with IgA nephropathy is a rare entity and limited literature regarding this is available [12]. Two possibilities may occur: MPO+ AAV showing features of IgA nephropathy in biopsy [13] or a biopsy proven IgA nephropathy patient develops MPO+ AAV with pauci immune picture on next biopsy [14].

O'Donoghue observed that 2% of patients with IgA nephropathy showed serum IgG-ANCA positivity [15]. Haas et al. reported findings on six ANCA-positive patients with IgAN, with crescents in more than 50% of glomeruli. The cases resembled ANCA-associated crescentic glomerulonephritis in both histological features and response to aggressive immune suppressive therapy [16]. Bantis et al. Observed eight ANCA-positive patients with IgAN, with more than 10% crescentic glomeruli, and reported more severe clinical manifestations and histological lesions, but better response to therapy, when compared with ANCA-negative patients [17]. Gabriel et al in their 4 patient case series of ANCA IgA overlap showed that 75% patients had eGFR <15, rapidly falling renal function and proteinuria where treated in the lines of severe vasculitis and showed good response to aggressive immunosuppression [18]. Cristiane Bitencourt Dias et al in their 5 patient case series showed a mean sub nephrotic proteinuria, 100% haematuria and mean creatinine of 2.2, 80% were c ANCA positive while all had normal complement levels [19]. Wenchao li et al compared the clinicopathologic features and prognosis of ANCA positive and ANCA negative IgA nephropathy nd found that ANCA positive patients had milder renal inflammation, higher ANA positivity rate and few immune deposits. ANA positive proved to be a poor independent prognostic factor. Renal outcome was similar between ANCA positive and negative IgA nephropathy in this study [20].

ANCA detection rate has been varied in various study cohorts ranging from 2.9% to 48%. This may be due to the method used for detection as some used immunofluorescence while others used ELISA. The presence of ANCA is a rare phenomenon in IgA nephropathy though the Clinicopathological picture is similar in both. In isolated crescentic IgAN, role of immunosuppression is doubtful and only a few RCT exist. Some studies have shown good response to Immunosuppression in ANCA positive cases while others show poor response. The difference may be because all ANCA might not be pathogenic [21].

Whether such concurrence is merely coincidental or has a role in pathogenesis/ predisposition for the other is not yet established. ANCA-associated (pauci-immune) crescentic GN is characterized by lesser endocapillary hyper cellularity and more disruption of Bowman's capsule than immune complex-related crescentic GN [22]. Treatment of crescentic IgA nephropathy has been less successful than pauci immune crescentic GN when given similar therapy; hence possibility of a favourable outcome stands in patients of IgA nephropathy who are MPO positive [23]. Treatment has been done in the lines AAV in most previous reports with successful outcome, also the presence of systemic vasculitis favours the role of MPO antibodies and role of maintenance therapy.

4.1 Strength and Limitations

It is a single case report. Long term follow up is not yet completed whether the disease would progress further.

5. CONCLUSION

Although KDIGO suggests to initiate treatment of AAV on basis of serology and clinical picture, biopsy is a must whenever clinical condition allows as such variants may be detected in biopsy only. Similarly, anti-MPO and anti-PR3 serological tests should be done in all cases if a renal biopsy shows a necrotizing and/or crescentic GN with glomerular IgA deposits, particularly if there is limited mesangial and endocapillary hypercellularity. A positive anti-MPO and/or anti-PR3 serological

test result in association with such a lesion may be responding better to corticosteroid and cytotoxic therapy. Further investigations are needed to study the role of ANCA in the development and progression of IgAN, whether the presence of ANCA is merely co incidental or the damage caused by IgAN results in neutrophil priming and generation of ANCAs.

6. DECLARATION

- Ethics approval and consent to participate: This study has been reviewed by the IPGME&R research oversight ethics committee and has therefore been performed in accordance with the ethical standards laid down in an appropriate version of the Declaration of Helsinki (as revised in Brazil 2013).
  This patient gave her informed consent prior to her inclusion in the study.
- Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

It is hereby declared that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this case report.

CONSENT and ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Treatment of IgA nephropathyBarratt, J. et al.Kidney International. 69(11):1934 – 1938.
   Available:https://doi.org/10.1038/sj.ki.5000419
2. Syed R, Rehman A, Valecha G, El-Sayegh S. Pauci-Immune Crescentic Glomerulonephritis: An ANCA-Associated vasculitis. Biomed Res Int. 2015;2015:402.
   Available:https://doi.org/10.1155/2015/402826
3. Haas M, Jafri J, Bartosh SM et al. ANCA-associated crescentic glomerulonephritis with mesangial IgA deposits. Am JKidney Dis 2000;36:709–718
4. Bantis C, Stangou M, SchlaugatCetal. Is presence of ANCA in crescentic IgA nephropathy a coincidence or novel clinical entity? A case series. Am J Kidney Dis 2010;55:259–268.
5. Allmaras E, Nowack R, Andrassy K. Rapidly progressive IgA nephropathy with anti-myeloperoxidase antibodies benefits from immunosuppression. Clin Nephrol 1997;48:269–273.
6. Tumlin JA, Lohavichan V, Hennigar R. Crescentic, proliferative IgA nephropathy: clinical and histological response to methylprednisolone and intravenous cyclophosphamide. Nephrol Dial Transplant. 2003;18(7):1321-9.
   Available:https://doi.org/10.1093/ndt/gfg081
7. Austin K, Janagan S, Wells M, Crawshaw H, McAdoo S, Robson JC. ANCA Associated vasculitis subtypes: Recent Insights and Future Perspectives. J Inflamm Res. 2022;15:2567-2582.
   Available:https://doi.org/10.2147%2FJIR.S284768
8. Nephrology Dialysis Transplantation. 2023;38(11):2637–2651.
   Available:https://doi.org/10.1093/ndt/gfad090
9. Augusto JF, Langs V, Demiselle J, Lavigne C, Brilland B, Duveau A. Low serum complement c3 levels at diagnosis of renal ANCA-associated vasculitis is associated with poor prognosis. PLoS ONE. 2016; 11(7):e0158871.
   Available:https://doi.org/10.1371/journal.pone.0158871
10. Gutiérrez E, Carvaca-Fontán F, Luzardo L, Morales E, Alonso M, Praga M. A personalized update on IgA nephropathy: a new vision and new future challenges. Nephron. 2020;144(11):555-71.
    Available:https://doi.org/10.1159/000509997
11. Ari Shimizu, Takashi Takei, Takahito Moriyama, Mitsuyo Itabashi, Keiko Uchida, Kosaku Nitta, Clinical and pathological studies of IgA nephropathy presenting as a rapidly progressive form of glomerulonephritis, internal medicine. 2013;52(22):2489-2494.
    Available:https://doi.org/10.2169/internalmedicine.52.0420
12. Yang YZ, Shi SF, Chen YQ, Chen M, Yang YH, Xie XF, Zou R, Lv JC, Liu LJ, Zhang H.

Clinical features of IgA nephropathy with serum ANCA positivity: a retrospective case-control study. Clin Kidney J. 2015;8(5):482-8.
Available:https://doi.org/10.1093%2Fckj%2Fsfv078

13. Yasukawa M, Kitagawa S, Togashi R, Asakawa S, Nagura M, Arai S, Yamazaki O, Tamura Y, Kondo F, Ohashi R, Uchida S, Shibata S, Fujigaki Y. A patient with mpo-anca-positive iga nephropathy diagnosed with the clinical onset of macrohematuria. Intern Med. 2019;58 (14):2051-2056.
Available:https://doi.org/10.2169%2Finternalmedicine.2475-18
14. Natalia Chebotareva, Elena Kamyshova, Nikolay Bulanov, Lidia Lysenko, Sergey Moiseev, Antineutrophil cytoplasmic autoantibody (ANCA) positive immunoglobulin A (IgA) nephropathy: Case reports and review of literature,The Egyptian Rheumatologist. 2020;42(3): 251-254,
ISSN 1110-1164.
Available:https://doi.org/10.1016/j.ejr.2020.06.002
15. O'Donoghue DJ, Nusbaum P, Noel LH. Antineutrophil cytoplasmic antibodies in IgA nephropathy and HenochSchonlein purpura. Nephrol Dial Transplant. 1992; 7:534–538.
16. Haas M, Jafri J, Bartosh SM et al. ANCA-associated crescentic glomerulonephritis withmesangial IgA deposits. Am JKidney Dis 2000;36:709–718.
17. Bantis C, Stangou M, SchlaugatCetal. Is presence of ANCA in crescentic IgA nephropathy a coincidence or novel clinical entity? A case series. Am J Kidney Dis 2010;55: 59–26818. Savige J, Davies D, Falk RJ, Jennette JC, Wiik A: Antineutrophil cytoplasmic antibodies and associated diseases: A review of the clinical and laboratory features. Kidney Int. 2000;57:846-862.
18. Ștefan G, Terinte-Balcan G., Stancu S. IgA nephropathy with serum ANCA positivity: Case series and literature review. Rheumatol Int. 2021;41:1347–1355.
Available:https://doi.org/10.1007/s00296-021-04888-2
19. Dias CB, Jorge LB, Woronik V, Cavalcante LB, Yu L. IgA nephropathy in patients with serum anti-neutrophil cytoplasmic autoantibody (ANCA) positivity: Case series. J Bras Nefrol. 2022;44(1):42-47.
DOI: 10.1590/2175-8239-JBN-2021-0018.
20. Wenchao Li, Ruifan Chen, Wei Chen, Fengxian Huang, Xi Xia; Clinicopathological features and outcomes of iga nephropathy with serum antineutrophil cytoplasmic autoantibody positivity. *Am J Nephrol* 27 November 2023;54(9-10):416–424.
Available:https://doi.org/10.1159/000533982
21. Huang X, Wang Y, Xie L, Zhang Y, Tang S, Yin S. IgA nephropathy with antineutrophil cytoplasmic antibody seropositivity. Clin Nephrol. 2015;84(3):156–64.
22. Roccatello D, Ferro M, Coppo R, Giraudo G, Quattrocchio G, Piccoli G. Report on intensive treatment of extracapillary glomerulonephritis with focus on crescentic IgA nephropathy. Nephrol Dial Transplant. 1995;10(11):2054-9.
23. Lv J, Yang Y, Zhang H, Chen W, Pan X, Guo Z, Wang C, Li S, Zhang J, Zhang J, Liu L, Shi S, Wang S, Chen M, Cui Z, Chen N, Yu X, Zhao M, Wang H. Prediction of outcomes in crescentic IgA nephropathy in a multicenter cohort study. J Am Soc Nephrol. 2013;24(12): 2118-25.
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