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Case Presentation

Atypical Anti-GBM with ANCA Vasculitis- A Rarest of the Rare Entity: Index Case from Eastern India

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Abstract

Anti-glomerular basement membrane (GBM) antibody glomerulonephritis is an extremely rare glomerular disease. Around 90% of the patients are positive for serum anti-GBM antibodies while up to 10% can be negative. In such patients, only a kidney biopsy can reveal the anti-GBM disease it is then labeled as an atypical anti-GBM disease. Though anti-GBM disease can be associated with Anti Neutrophil Cytoplasmic Antibodies (ANCA) positivity, it is extremely rare to find atypical anti-GBM with ANCA positivity so much so that till now there are very few such cases reported from across the world.

The case presented here is one such case where the patient presented with adult-onset nephrotic syndrome features with active urinary sediments and mildly deranged renal function. Myeloperoxidase (MPO) ANCA was positive and it was considered ANCA-associated crescentic glomerulonephritis (GN) but after the renal biopsy the picture was of anti-GBM disease. She was treated with pulse methylprednisolone but her creatinine increased in the meantime and considering anti-GBM she was put on Plasma Exchange (PLEX). She received 5 sessions of PLEX after which her renal function improved. She was also planned for Rituximab which could not be given due to local infection.

As there are no protocols for treating such cases because of the extremely rare nature of the presentation, this case will increase the understanding of such presentations for the clinicians. This will help to plan for building the approach for such cases.

More Information

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Abbreviations: GBM: Glomerular Basement Membrane; ANCA: Anti Neutrophil Cytoplasmic Antibodies; PLEX: Plasma Exchange; ARB: Angiotensin Receptor Blocker; JMS: Jones Mehenamine Silver; PAS: Periodic Acid Schiff; DIF: Diffuse Immunofluorescence

Introduction

Anti-glomerular basement membrane (GBM) antibody glomerulonephritis is an extremely rare glomerular disease with the incidence being 0.5-1 per million population. Though the immunoassays for anti-GBM antibodies are positive in around 90% of the patients [1], they may be absent in up to 10% of patients. These are labeled as atypical anti-GBM disease and in such patients, the diagnosis can be established only by kidney biopsy. Atypical anti-glomerular basement membrane (anti-GBM) disease is characterized by linear immunoglobulin G (IgG) deposition along the GBM in the absence of circulating IgG anti-GBM antibodies. Whereas the classic anti-GBM disease is more aggressive in nature, the atypical one is milder usually [2]. Double positivity for anti-GBM and ANCA can also be found and around 47% of patients with seropositive anti-GBM disease were also positive for ANCA and 5-14% of patients with AAV tested positive for anti-GBM antibody [2-4]. There are very few cases of atypical anti-GBM with ANCA positivity and no such case has been reported from India before in the literature.

The case presented here is one such case and it is even more intriguing as it presented with nephrotic range proteinuria and serum creatinine not being too high but diffuse crescentic GN on renal biopsy.

Case presentation

Thirty-three-year-old married female with no previous comorbidities presented to us in the Nephrology Outpatient Department of IPGME&R and SSKMH, Kolkata, West Bengal (India) with bipedal swelling associated with foamy urine from the last 2 months. She also had a history of cough without sputum and fever without chills or evening rise 2 months back before the onset of swelling which subsided within a week with some OTC medications. She also had reddish discoloration of urine a few times in these 2 months. Her symptoms were not associated with decreased urine

output, burning micturition, blood-tinged sputum oral ulcers, photosensitivity, rash, or joint pain. She had no living issues and no pregnancy loss. On examination, her pulse was 84 bpm, and saturation at room air was 99%. Her blood pressure at presentation was 126/84 mm Hg. Pallor and bipedal pitting edema up to the knees was present. Normal vesicular breath sounds were present all over the lung fields except in the bilateral infra-axillary and infrascapular area where the sounds were diminished. Her baseline investigations revealed the following: Hemoglobin-10.0 g/dl, total counts 9000/cumm platelets 1.6L/cumm, urea 38 mg/dl, creatinine 1.43 mg/dl, albumin 2.32 g/dl, sodium 143 mmol/L and potassium 4.2 mmol/L. Immunological profile was done which came out as C3 158, C4 65.3, ANA(Hep2)-Negative, Anti PLA2R(ELISA)-negative, ANCA- pANCA positive, MPO-106 and PR3- negative. Urine examination showed albumin 2+, occult blood 2+ and 6-7 RBCs, and 9.8 g/day proteinuria. A chest X-ray was done which did not reveal any significant abnormality except bilateral pleural effusion. On ultrasonography, both the kidneys were of normal size with slightly raised cortical echogenicity, and corticomedullary differentiation was maintained. 2-D echocardiography was also done and it had no regional wall motion abnormalities with normal valves and a 65% ejection fraction. With high titre MPO positivity but Nephrotic syndrome presentation and renal function not much deranged, she underwent a renal biopsy which revealed the following:

Light Microscopy (Figures 1,2) - 8 Glomeruli, one segmentally sclerosed with Adhesion formation, rest 7 show mild mesangial matrix and focal mesangial hypercellularity. A total of 5 glomerulus show fibrocellular crescent formation amongst which two are circumferential and three are segmental in nature. Capillary loops are open, and GBM is fragmented at the site of crescent formation. Tubules - mild atrophy noted. Preserved tubules show acute tubular injury. Vesselsarteriosclerosis noted. Interstitium- mild fibrosis noted. Multifocal lymphocytic infiltration was noted in the scarred Interstitium. IF/TA 10% Immunofluorescence (Figure 3) - 12 Glomeruli, IgG 2+ linear positivity along the capillary wall, IgA negative, IgM Segmental mesangial entrapment in 3 glomeruli, C3c negative, C1q Negative, Kappa trace linear positivity along the capillary wall, and Lambda-Negative.

In the due course her creatinine kept on increasing and peaked to 2.35 mg/dl and hemoglobin to 9.6 g/dl and treatment was started with IV pulse methylprednisolone 500mg once daily for 3 doses f/b oral steroid. She was declared atypical anti-GBM with ANCA and she was put on PLEX. We provided 5 sessions of PLEX on alternate days and was planned for rituximab injection but it could not be given due to local infection in the lower limbs and deferred till the resolution of the infection. Her creatinine continued declining and she kept improving. She was discharged after around 4 weeks of admission with hemoglobin 10.2 g/dl and creatinine of 1.3 mg/dl with oral steroids (prednisolone), antibiotics (oral 3rd generation cephalosporin), antiproteinuric (ARB), a loop diuretic, calcium, and statin and is due for injection rituximab. She has been asked to follow up in our Outpatient Department for further treatment Tables 1,2.

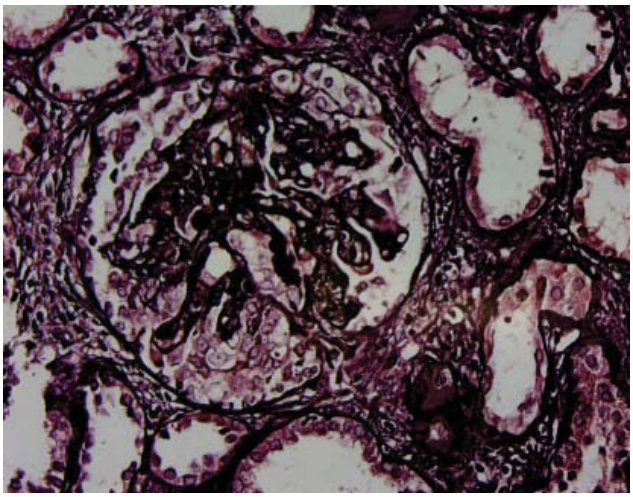

Figure 1: Light Microscopy (JMS-400X) showing crescentic changes in a glomerulus

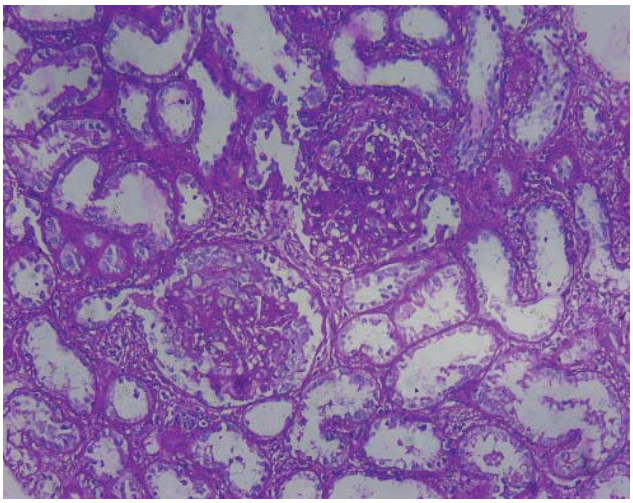

Figure 2: Light Microscopy (PAS-100X) showing crescentic changes in glomeruli

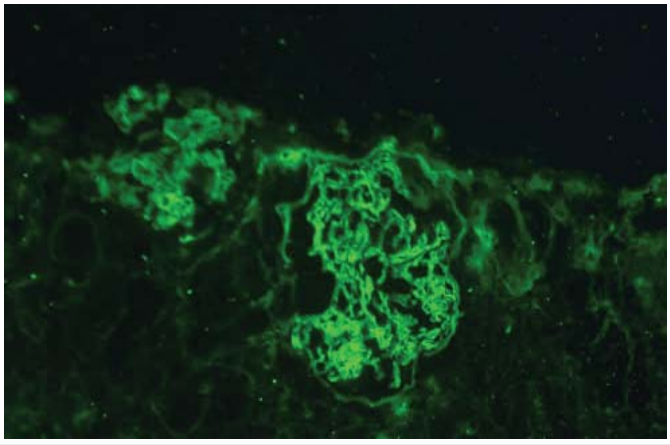

Figure 3: DIF (200X) showing linear positivity for IgG along the capillary wall

Table 1: Blood parameters at baseline and follow-up.

Parameter (normal range)	Baseline	1st follow up (before PLEX)	2nd follow up (After PLEX)
Hemoglobin (12-15g/dl)	10.0	9.6	10.2
T.L.C.(4000-11000/cumm)	9000	13600	17300
Platelets (1.5-4.1 lakhs/cumm)	1.6	1.43	1.49
Sodium(135-145 mEq/l)	143.0	Not done	139.6
Potassium (3.5-5.1 mEq/l)	4.2	Not done	4.11
Albumin (3.5-5.2 g/dl)	2.32	2.5	2.8
Urea (21-43 mg/dl)	38.0	54.5	27.0
Creatinine (0.7-1.1 mg/dl)	1.43	2.35	1.30

Table 2: Immunological markers in serum.

Parameter(normal range* with units)	Values
C3(90-180 mg/dl)	158
C4(10-40 mg/dl)	65.3
ANA(by hep 2)	Negative
ANCA	Positive
MPO(< 2 U/ml)	106
PR3(< 2 U/ml)	< 2
Anti-GBM antibodies (IFA)	Negative
Anti PLA2R Antibody(IU/ml by ELISA)	< 14

*Wherever applicable

Discussion

Though the double positive disease is found, the overlap of atypical anti-GBM with MPO/PR3 positivity is extremely rare to find and to date, there are few case reports available in the literature of such a rare case with none of them coming from India. Guo, et al. Reported one such case of a patient with an atypical anti-GBM disease whose serum was negative for the anti-GBM antibody but positive for the myeloperoxidase (MPO) anti-neutrophil cytoplasmic antibody (p-ANCA) and another atypical ANCA. Laboratory test results showed severe renal insufficiency. Renal biopsy specimen analysis revealed 100% glomeruli with crescents; immunofluorescence showed immunoglobulin G (IgG) linearly deposited alongside the GBM. Finally, the patient was discharged successfully after treatment with plasmapheresis, methylprednisolone, and prednisone [5].

A major cause of nondetection of anti-GBM antibodies in serum is the trapping of these antibodies in kidneys or lungs though other causes are also described. The tests available for detection are ELISA-based and do not guarantee 100% sensitivity and specificity [6] so more advanced tests can increase the chances of detection of these antibodies. Due to the very rare occurrence of such a scenario, there are no clear guidelines to treat such patients.

Despite the presence of more than 50% of crescents in this biopsy the course of our patient was not so stormy. As is the case in double-positive patients [7], this patient was also treated with Plasma exchange and high-dose steroids, and the positive response of pulse steroids and PLEX in such a patient proves that treating such a patient on the lines of anti-GBM is fruitful. As the peak serum creatinine was 2.35 and it also started to come down after starting the immunosuppression, a decision to go with cyclophosphamide was withheld and rituximab was planned.

The patient will be followed up further in our institute and will be monitored for the long-term outcome of the disease.

Conclusion

As there are no protocols for treating such cases because of the extremely rare nature of presentation which might be due to the nondetection of anti-GBM antibodies due to limitations of currently available techniques or maybe because of the actually rare nature of such a case, this case will increase the understanding of such presentations for the clinicians. This will also help to plan for building the approach for such cases. Further follow-up of this patient will also help us understand the role of rituximab in such a clinical scenario.

Ethical declarations

This case report has been prepared in accordance with the revised Declaration of Helsinki and informed patient consent has been taken from the patient for the publication and presentation of the data. No AI tools have been used for preparing or producing this case report. There is no funding from any source and there is no conflict of interest of the corresponding author or the co-authors.

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