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An uncommon histologic pattern of anti-GBM glomerulonephritis; focal crescentic and necrotizing pattern

Ahmad Altaleb[1*], Hani Nawar[2]

[1]Department of Histopathology, Mubarak Al-Kabeer Hospital, Jabriya, Kuwait
[2]Department of Nephrology, Jahra Hospital, Jahra, Kuwait

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ABSTRACT

Anti-glomerular basement membrane (anti-GBM) disease is a rare small-vessel vasculitis that involves glomerular capillaries, pulmonary capillaries or both, with anti-GBM autoantibody deposition along the GBM. It typically presents with alveolar hemorrhage and rapidly progressive crescentic glomerulonephritis that progresses abruptly to end-stage renal failure if untreated. Autoantibodies targeting the alpha-3 chain of type IV collagen mediate the disease in glomerular and alveolar basement membranes. Histologically, the kidneys generally display diffuse necrotizing and crescentic glomerulonephritis. This case report highlights the case of a 20-year-old man who was admitted with a working diagnosis of pulmonary renal syndrome. His anti-GBM antibodies result came out at a level of 200 U/mL (normal level < 20 U/mL). The renal biopsy findings were unusual as it showed glomeruli with only 11% cellular crescents and 7% tuft fibrinoid necrosis. In addition, by immunohistochemical studies, the biopsy reveled a strong IgG and IgA signals by immunoperoxidase method, which is another unusual finding in the setting of anti-GBM glomerulonephritis. The final renal biopsy diagnosis was focal necrotizing and crescentic glomerulonephritis (with 11% cellular crescents) compatible with anti-GBM glomerulonephritis. This case demonstrates the paramount importance of clinicopathological correlation when interpreting medical renal biopsies.

Case Report

Implication for health policy/practice/research/medical education:
In this case report we describe an uncommon histologic pattern of anti-glomerular basement membrane (anti-GBM) glomerulonephritis. This emphasizes the importance of clinicopathologic correlation when assessing renal biopsies in the setting of medical renal diseases.

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Introduction

Anti-glomerular basement membrane (anti-GBM) disease is a rare small-vessel vasculitis that involves glomerular capillaries, pulmonary capillaries or both, with anti-GBM autoantibody deposition along the GBM. In general, anti-GBM disease is a term used for any clinical expression of disease caused by anti-GBM antibodies and comprises isolated anti-GBM pulmonary hemorrhage, Goodpasture syndrome, and isolated anti-GBM glomerulonephritis (1). Currently, the preferred term is anti-GBM disease as atypical forms of this disease exists (2). Most patients present with alveolar hemorrhage and rapidly progressive crescentic glomerulonephritis that, progresses quickly to end-stage kidney disease if untreated (3).

The incidence of the disease shows some geographic variation, with estimations documented to be 0.5, 1.8, and 10 cases per million populations per year in European, Asian and American populations, respectively (4-7).

Anti-GBM disease exhibits a bimodal age distribution, with a peak incidence in the third decade of life, when there is a slight male predominance, and in the sixth decade, when it affects primarily females. In addition, it has been observed that younger patients are more frequently presenting with lung involvement, while older patients tend to present with isolated renal involvement (8-12).

Anti-GBM disease is by and large a disease of unknown etiology. Nevertheless, there is increasing evidence that genetic susceptibility to anti-GBM disease is present, in particular in cases with HLA-DR15 and -DR4 (13). In

*Corresponding author: Ahmad Altaleb,
Email: dr.afaltaleb@gmail.com

addition, various triggers causing renal or pulmonary injury, that favor the release of increased amounts of auto-antigen, have been illustrated. Possible triggers of lung damage include smoking, pulmonary infections, hydrocarbon solvent exposure and lung cancer (14). Recently, during the COVID-19 pandemic, Prendecki et al identified novel clusters of anti-GBM disease in association with SARS-CoV-2 infection, suggesting that viral infection as a trigger for secondary autoimmunity and supporting the connotation amongst pulmonary damage and anti-GBM disease development (15).

Possible triggers of kidney injury include ureteral obstruction, lithotripsy, membranous nephropathy, and ANCA-related glomerulonephritis (2,16).

The glomerular basement membrane consists of a network of type IV collagen molecules, each made up of triple-helical protomers of α3, α4, and α5 chains. The main target of the autoimmune response in anti-GBM disease has been identified as the non-collagenous (NC1) domain of the α3 chain of type IV collagen (α3[IV]NC1; the "Goodpasture autoantigen" (2).

Moreover, T cells appear to play a role in the disease pathogenesis. Animal models' data propose that T cells may contribute directly to cell-mediated glomerular injury, that can occur without any substantial humoral immunity (17,18).

The mainstay of treatment is plasma exchange and immunosuppressive agents. The most recent Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend the administration of immunosuppression with cyclophosphamide and glucocorticoids plus plasmapheresis in all patients with anti-GBM except those who need dialysis at presentation, have 100% crescents or >50% global glomerulosclerosis, and do not have pulmonary hemorrhage. Treatment should be initiated without delay if this diagnosis is suspected, even before the confirmed diagnosis (19).

The key histopathologic findings in acute anti-GBM glomerulonephritis are glomerular fibrinoid necrosis and crescent formation. In the setting of anti-GBM glomerulonephritis, approximately 80% of glomeruli have crescents; however, this ranges from less than 5% up to 100%. The classic immunohistochemistry finding is linear staining of glomerular basement membranes for IgG, usually accompanied by much lesser signal of granular to discontinuous linear staining for C3 (20).

Case Presentation

A 20-year-old male with no significant past medical history presented for evaluation. He is a cigarette smoker and works as a firefighter trainer. The patient reported symptoms of cough, shortness of breath, and hemoptysis. Upon examination, he appeared pale and exhibited tachypnea and tachycardia; however, he remained clinically stable with oxygen saturation levels maintained within normal ranges in ambient conditions. His labs showed raised serum creatinine (100 µmol/L from a baseline of 70 µmol/L few months earlier), low hemoglobin (79 g/L) and urine routine showed proteinuria and hematuria (with some RBCs casts). His chest X-ray revealed bilateral diffuse infiltration shadow.

The patient was admitted with a working diagnosis of pulmonary renal syndrome. His immunology workup (including ANA, pANCA, cANCA, Anti dsDNA Abs, C3 and C4) was normal. Moreover, the virology workup (HCV Abs, HBsAg and HIV Abs) was negative. Immune hemolytic indices, and coagulation profile were all normal. Pelviabdominal ultrasound was unremarkable. High resolution computed tomography scan and bronchoscopy documented pulmonary hemorrhage. One day after the bronchoscopy, anti-GBM antibodies result came out at a level of 200 U/mL (normal level<20 U/mL). The diagnosis was confirmed as anti-GBM related pulmonary renal syndrome (Goodpasture syndrome).

The patient was initiated on pulse methylprednisolone at a dosage of 1 g/day for three consecutive days. This was followed by oral prednisolone at a dose of 1 mg/kg/d. Additionally, the patient underwent daily plasma exchange (PLEX), exchanging 4 liters with a 5% albumin replacement fluid daily for 14 days, along with cyclophosphamide (2 mg/kg/d PO).

Over the first three days of hospitalization, his serum creatinine level remained stable at the same level of 100 umol/L. According to the persistent hematuria and proteinuria of 5 g/24 h kidney biopsy was obtained after the first session of PLEX.

The kidney biopsy consisted of two cores of renal tissue containing 27 glomeruli, none of which were globally sclerotic. A maximum of three cellar crescents (11%) were present, and two glomeruli revealed tuft necrosis (7%) (Figures 1and 2). No endocapillary or mesangial hypercellularity was observed and the the glomerular capillary walls appeared normal by light microscopy. The tubulointerstitium showed acute tubular injury and numerous red cell casts were present. There was no significant interstitial fibrosis, inflammation or tubular atrophy. Immunoperoxidase studies revealed linear IgG and IgA positivity with signal intensities of 2+ and 1 to 2+, respectively (Figures 3 and 4). IgM, C3c and C1q were negative.

Therefore, the final diagnosis was focal necrotizing and crescentic glomerulonephritis, with 11% cellular crescents, consistent with anti-GBM glomerulonephritis.

Table 1 shows the serum anti-GBM Abs levels during therapy. The initial anti-GBM level before starting PLEX was 200 U/L. After the 7th session of PLEX, which

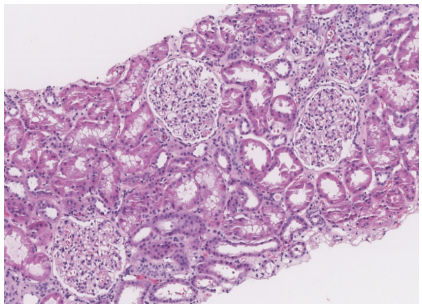

Figure 1. Renal biopsy showed several spared glomeruli with no evidence of crescentic or necrotizing lesions [H&E stain] (×10).

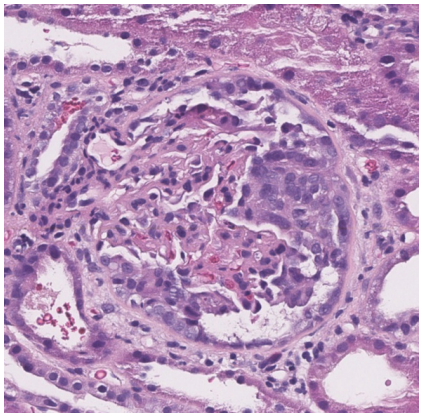

Figure 2. Partial cellular crescent abutting the tubular pole with a rather compressed glomerular tuft [H&E stain] (×40).

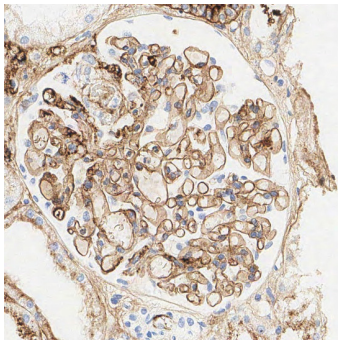

Figure 3. IgG immunohistochemical stain shows linear staining along the capillary walls. [immunoperoxidase technique] (×40).

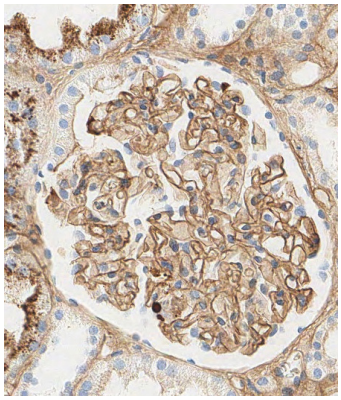

Figure 4. IgA immunohistochemical stain shows linear staining along the capillary walls. [immunoperoxidase technique] (×40).

coincided with the kidney biopsy, the anti-GBM level dropped significantly to 26 U/L. It continued to decrease, reaching 14 U/L after the 14th session of PLEX. The last recorded anti-GBM level was 25 U/L, taken one week after the final session.

Discussion

Anti-glomerular basement membrane disease is a rare small-vessel vasculitis that involves glomerular capillaries, pulmonary capillaries or both, with anti-GBM autoantibody deposition along the GBM (1).

The key histopathologic findings in acute anti-GBM glomerulonephritis are glomerular fibrinoid necrosis and crescent formation. According to the World Health Organization (WHO), glomerular crescent is defined as two or more layers of cells that are partially or completely filling the Bowman space. In the setting of anti-GBM glomerulonephritis, on average, approximately 80% of glomeruli have crescents; however, this ranges from less than 5% up to 100%. These crescents may be segmental or circumferential that may extend into the origin of the renal proximal tubule. The composition of crescents in anti-GBM glomerulonephritis can range from layers of cells with epithelial appearance where they form orderly layered crescents, to very disorderly crescents primarily made up of macrophages/other inflammatory cells with or without multinucleated giant cells (20).

The present case was unusual from the morphological

Table 1. Serum anti-GBM antibody levels during therapy

Anti-GBM levels (U/L)	Timing
200	At the time of diagnosis before PLEX
26	After 7th session of PLEX (around the time of the kidney biopsy)
14	After 14 sessions of PLEX
25	One week after the last PLEX session

point of view, as the renal biopsy contained 27 glomeruli, only 3 of which (11%) displayed cellular crescents and 2 (7%) exhibited tuft fibrinoid necrosis. In 2009, Gowrishankar et al reported an interesting case of anti-GBM disease manifested as thrombotic microangiopathy (TMA) and without crescents (21). However, there is no published report of any case of anti-GBM glomerulonephritis with very focal crescent formation.

The classic immunohistochemical finding in anti-GBM glomerulonephritis is linear staining of glomerular basement membranes for IgG, usually accompanied by a much lesser signal of granular to discontinuous linear staining for C3 (20).

Another interesting and unusual finding in our case is revealed by immunohistochemical studies which was manifested as strong IgA signal (besides strong IgG signal) by immunoperoxidase method.

Minority of anti-GBM disease cases may show IgA and IgM linear staining, but with a much weaker signal than IgG. However, rare patients with anti-GBM disease may show isolated linear glomerular staining only for IgA and have circulating IgA anti-GBM antibodies in the absence of IgG anti-GBM antibodies in the serum or glomerular depositions (22-24). Meanwhile, Borza and others, reported a peculiar case of a 62-year-old man with recurrent Goodpasture's disease secondary to an autoreactive IgA antibody. The kidney biopsy from the native and subsequently allograft kidneys showed focal crescentic glomerulonephritis with strong linear staining for IgA and κ light chains along glomerular, tubular, and Bowman's capsule basement membranes (25).

Of note, the reported cases utilized immunofluorescence method rather than immunoperoxidase method for the immunohistochemical study of renal biopsies. In our case we have used immunoperoxidase method. Issues pertaining to sensitivity and specificity should be considered although they seem insignificant from our experience.

Conclusion

This case demonstrates the importance of clinicopathologic correlation whenever interpreting medical renal biopsies. Pathologist should always correlate with clinical and laboratory tests findings before rendering any diagnosis of glomerulonephritis. Also, pathologists should be more pragmatic when interpreting renal biopsies for medical renal diseases as unusual cases can always exist.

Authors' contribution

Conceptualization: Ahmad Altaleb and Hani Nawar.
Data curation: Ahmad Altaleb and Hani Nawar.
Formal analysis: Ahmad Altaleb.
Investigation: Ahmad Altaleb and Hani Nawar.
Project administration: Ahmad Altaleb.
Resources: Ahmad Altaleb.
Writing–original draft: Ahmad Altaleb.
Writing–review & editing: Ahmad Altaleb.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

This study was conducted in accordance with the World Medical Association Declaration of Helsinki. The patient provided us with written informed consent for publication as a case report. Additionally, the authors have completely observed ethical issues (including plagiarism, data fabrication, and double publication).

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