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Seronegative Anti-Glomerular Basement Membrane Disease Presenting as Rapidly Progressive Glomerulonephritis: A Diagnostic Challenge from South India

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Abstract: ***Anti–glomerular basement membrane (anti-GBM) disease is a rare, fulminant autoimmune small-vessel vasculitis characterized by rapidly progressive glomerulonephritis (RPGN), with or without pulmonary haemorrhage. Detection of circulating anti-GBM antibodies is traditionally considered central to diagnosis; however, seronegative variants pose a significant diagnostic challenge, particularly in regions where infection-related and ANCA-associated glomerulonephritides are more prevalent. We report the case of a 45-year-old male from South India who presented with subacute onset bilateral pedal edema, facial puffiness, and progressive exertional dyspnoea. Laboratory evaluation revealed nephrotic-range proteinuria, active urinary sediment, and rapidly worsening renal dysfunction. Extensive serological evaluation, including anti-GBM antibodies, antinuclear antibodies, and ANCA, was negative. Given the clinical suspicion of RPGN, renal biopsy was performed and demonstrated crescentic glomerulonephritis with linear IgG deposition along the glomerular basement membrane on immunofluorescence, establishing the diagnosis of anti-GBM disease.***

Keywords: Anti-GBM disease; Goodpasture's disease; Rapidly progressive glomerulonephritis; Seronegative vasculitis; Crescentic glomerulonephritis

1. Introduction

Anti–glomerular basement membrane disease is a rare autoimmune disorder mediated by IgG autoantibodies directed against the non-collagenous domain of the α3 chain of type IV collagen, predominantly affecting renal and pulmonary capillary basement membranes. It classically presents as a pulmonary–renal syndrome but may manifest as isolated renal disease. In clinical practice, diagnosis is often guided by detection of circulating anti-GBM antibodies; however, seronegative cases are increasingly recognized. In regions such as Andhra Pradesh and Telangana, where RPGN is more commonly attributed to infection-related or ANCA-associated etiologies, seronegative anti-GBM disease is frequently under-recognized. We describe a biopsy-proven seronegative anti-GBM disease presenting as RPGN, emphasizing diagnostic pitfalls and region-specific differentials.

2. Case Report

A 45-year-old male, chronic smoker, presented with a history of **bilateral lower limb swelling of six months' duration**, associated with **progressive exertional dyspnoea**, which had worsened over the preceding fifteen days. The dyspnoea corresponded to **New York Heart Association functional class II** and was not associated with orthopnoea or paroxysmal nocturnal dyspnoea. He also noted **facial puffiness**, particularly in the early morning hours.

There was **no history of fever, recent upper respiratory tract or skin infection**, haemoptysis, cough, wheeze, chest pain, oliguria, or gross haematuria. The patient denied **skin rash, oral ulcers, photosensitivity, joint pains, or constitutional symptoms**, thereby reducing the likelihood of connective tissue disease–associated nephritis. There was no prior history of diabetes mellitus, hypertension, chronic kidney disease, tuberculosis, or exposure to nephrotoxic

drugs. He had no history of recent vaccination or intake of indigenous medications.

On examination, the patient was conscious and oriented. He was **hypertensive** and had **bilateral pitting pedal edema (grade 2)**. There was no pallor, icterus, cyanosis, clubbing, lymphadenopathy, or cutaneous purpura. Cardiovascular examination revealed normal heart sounds without murmurs. Respiratory system examination showed clear lung fields, with no crackles or wheeze. Abdominal and neurological examinations were unremarkable.

Initial laboratory investigations revealed a **normal complete blood count**. Urinalysis showed **albuminuria (++++)**, **microscopic haematuria (15–18 red blood cells per high-power field)**, and **5–6 pus cells per high-power field**, with no casts. Twenty-four-hour urinary protein excretion was **2.74 g/day**. Renal function tests demonstrated **blood urea of 63 mg/dL** and **serum creatinine of 4.3 mg/dL**, indicating significant renal impairment. Ultrasonography of the abdomen revealed **bilaterally enlarged kidneys with increased parenchymal echogenicity**, suggestive of intrinsic renal disease.

Given the clinical picture of **rapidly progressive glomerulonephritis**, an extensive serological workup was performed. **Anti-GBM antibodies, antinuclear antibodies, anti-double-stranded DNA antibodies, and antineutrophil cytoplasmic antibodies** were all negative. In view of worsening renal function despite negative serology, a **renal biopsy** was undertaken.

Histopathological examination revealed **crescentic glomerulonephritis** on light microscopy. Immunofluorescence microscopy demonstrated **linear IgG deposition along the glomerular basement membrane**, a finding pathognomonic of anti-GBM disease. Based on these findings, a final diagnosis of **seronegative anti-glomerular basement membrane disease** was established.

3. Discussion

Anti-GBM disease represents a prototypical antibody-mediated autoimmune glomerulonephritis, characterized by rapid destruction of the glomerular basement membrane. The pathogenic antibodies are directed against the NC1 domain of the α3 chain of type IV collagen, leading to complement activation and crescent formation. Traditionally, detection of circulating anti-GBM antibodies has been considered essential for diagnosis; however, up to 10% of cases may be seronegative, as demonstrated in this patient.

Seronegative anti-GBM disease presents a significant diagnostic challenge, particularly in low- and middle-income countries such as India. In Andhra Pradesh and Telangana, RPGN is more frequently attributed to infection-related glomerulonephritis, diabetic nephropathy with superimposed injury, or ANCA-associated vasculitis. Consequently, reliance solely on serological testing may delay diagnosis and definitive therapy.

The absence of pulmonary hemorrhage in this patient is consistent with renal-limited anti-GBM disease, a recognized but less common phenotype. Smoking has been implicated as a risk factor for alveolar basement membrane injury; however, pulmonary involvement is not universal. The lack of systemic features such as fever, rash, or arthralgia helped exclude lupus nephritis and systemic vasculitides. Negative ANCA testing reduced the likelihood of ANCA-associated crescentic glomerulonephritis, while the absence of hypocomplementemia and antecedent infection argued against post-infectious glomerulonephritis.

Renal biopsy remains the **gold standard** for diagnosis in suspected RPGN. The presence of **linear IgG staining along the glomerular basement membrane** on immunofluorescence is diagnostic of anti-GBM disease and distinguishes it from immune-complex–mediated and pauci-immune glomerulonephritides. Prognosis in anti-GBM disease is closely related to serum creatinine at presentation and the percentage of glomeruli exhibiting crescents. Early diagnosis and prompt initiation of therapy, including plasma exchange, corticosteroids, and cyclophosphamide, are critical determinants of renal survival.

This case reinforces an important clinical principle: **negative serology does not exclude anti-GBM disease**. In regions where RPGN is common and diagnostic resources may be limited, clinicians must maintain a high index of suspicion and pursue renal biopsy without delay when clinical features suggest a rapidly progressive course.

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