# Anti-Glomerular Basement Membrane Glomerulonephritis in an HIV Positive Patient: Case Report

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**We report on a case of a patient with HIV infection, diagnosed 18 months prior to the development of an anti-glomerular basement membrane (anti-GBM) rapidly progressive glomerulonephritis; this is probably the first report of such an association. A 30-year-old white man presented with elevation of serum creatinine (1.3 - 13.5 mg/dL within one month). At admission, the urinalysis showed proteinuria of 7.2 g/L and 8,000,000 erythrocytes/mL. Renal biopsy corresponded to a crescentic diffuse proliferative glomerulonephritis mediated by anti-GBM, and serum testing for anti-GBM antibodies was positive; antinuclear antibodies (ANA) and anti-neutrophilic cytoplasmic antibodies (ANCA) were also positive. The patient underwent hemodyalisis and was treated with plasmapheresis, cyclophosphamide and prednisone. The association described here is not casual, as crescentic glomerulonephritis is not common in HIV-positive patients, anti-GBM glomerulonephritis is rare and anti-GBM antibodies are frequently observed in HIV-positive subjects when compared to the overall population. Based on the current case and on the elevated frequency of the positivity for such antibodies in this group of patients, it is advisable to be aware of the eventual association between these two conditions and to promote an active search for anti-GBM antibodies and early diagnosis of eventual urinary abnormalities in HIV-positive subjects, considering the severity of anti-GBM glomerulonephritis.**

**Key Words: Anti-GBM glomerulonephritis, HIV, urinary abnormalities.**

Goodpasture's syndrome includes glomerulonephritis, lung hemorrhage and glomerular basement membrane antibodies (GBM) [1]. Lung hemorrhage occurs in 50 to 70% of the cases, with greater incidence in smokers. It may be determined or exacerbated by pulmonary infection or hypervolemia and can also occur in the absence of significant renal disease [2,3]. From an epidemiological point of view, HLA-DR15 seems to be the most important risk factor for the development of this disease. HLA-DR7 has also been related to the process, but it is considered to be less involved [4].

In the case of renal involvement, antibodies are strongly linked to the GBM in a linear pattern, and sometimes weakly to the Bowman's capsule and to the tubular basement membrane, as demonstrated by immunofluorescence. This technique is probably sensitive enough for identification of the antibodies, but it is not totally specific, as the linear pattern has already been demonstrated in kidney allografts, *diabetes mellitus*, systemic lupus erithematosus, fibrillary glomerulonephritis, and even in normal kidneys [2]. In addition, circulating anti-GBM autoantibodies can be demonstrated by several other available assays with different sensitivities and specificities [2,3].

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Lung hemorrhage is not a constant finding, both in patients and in experimental animal models, and it has a weak correlation with the serum levels of anti-GBM antibodies. Initially, it was thought that the pulmonary and the renal antigens were distinct. Recently, it has been demonstrated that the antigen is the same in both tissues. However, the accessibility of the antibody to the antigen is different in the two tissues. While a highly specific antibody to the basement membrane will link to the GBM after an intravenous injection, probably due to the fenestrated nature of the glomerular endothelium, there should be previous insult in the alveolus that exposes the antigen epitopes in order to allow binding to circulating antibodies. Therefore, there seems to be an association between toxicity by oxygen, smoking, organic solvents, infection and the development of lung hemorrhage [5,6]. Recently, it has been suggested that the exposition of the antigen by tissue injury might be the main pathogenic mechanism [7].

We report on a case of a patient with HIV infection, diagnosed 18 months prior to the development of an anti-GBM rapidly progressive glomerulonephritis. To the best of our knowledge, this is the first report of such an association.

## Case Report

A 30-year-old white man presented with a history of acute hepatitis B virus 18 months previously, when the diagnosis of HIV infection was also established and a year previously, secondary syphilis was diagnosed. At hospitalization, he presented with nephritic syndrome and acute renal failure. The serum creatinine increased from 1.3 to 13.5 mg/dL in one

month. At admission, the initial urinalysis showed proteinuria of 7.2 g/L and 8,000,000 erythrocytes/mL, with evident erythrocytic dismorfism and 30,000 leukocytes/mL. The patient had clinical and serological criteria of cured hepatitis B (negative HbsAg, positive anti-HBc IgG, negative HbeAg, positive anti-HBs) and for syphilis (positive VDRL 1/4 - decreasing titre, positive FTA-Abs). His initial blood count revealed hemoglobin 13.9g/dL, hematocrit 40%, leukocytes 7,100/mL, platelets 260,000/mL; a chest X-ray was normal; the physical examination revealed no alteration and his blood pressure was 120 x 80 mmHg. Ultrasonography showed both kidneys of normal size. He was submitted to a renal biopsy. Light microscopy showed eight glomeruli with focal fibrinoid necrosis, substantial endocapillary hypercellularity, a moderate degree of neutrophilic infiltration and circumferential cellular crescents in 50% of the sampled glomeruli; the intact capillary walls had normal thickness (Figure 1-3); in addition, there was moderate tubular acute necrosis; the immunofluorescence technique revealed linear fluorescent deposits of IgG and C3 along the GBM. In summary, the renal biopsy corresponded to a progressive diffuse proliferative glomerulonephritis mediated by anti-GBM. Serum testing for anti-GBM antibodies was positive, with a titer of 68 U/mL; serum tests for ANA and ANCA were positive; total complement activity was 160 UCH50/mL (reference value: 130 to 330), C2 98% (RV: > 70%), C3 116 mg/dL (RV: 90 to 180), C4 27 mg/dL (RV: 10 to 40), negative for anti-dsDNA, -RNP, -Sm, -Ro and -La, undetectable HIV viral load and $CD_4$ 495/mL (RV > 1,000). The patient underwent hemodyalisis and was treated with 14 sessions of plasmapheresis, a low dose of cyclophosphamide (1.5 mg/kg) and prednisone (1 mg/kg) for two weeks. The treatment was discontinued due to the persistence of signs and symptoms and development of leukopenia. The patient was maintained in dialysis and did not present any infectious complications or pulmonary symptomatology within a six-month follow-up period.

**Discussion**

HIV-positive patients may present with renal involvement related to the infection itself, to supervening infections or to the side effect of drugs used in treatment [8,9].

Several glomerulopathies have been observed in HIV-positive patients, such as IgA nephropathy, membranous glomerulonephritis, proliferative glomerulonephritis, minimal change disease, and particularly the collapsing variant of focal segmental glomerulosclerosis, which is an usual presentation of HIV-associated nephropathy [10-14].

We present a case of anti-GBM rapidly progressive glomerulonephritis in an HIV positive patient, an association that, to the best of our knowledge, has not been previously reported.

For treatment, considering the severity of the renal failure, we decided to use the same immunosuppressive regimen recommended for patients with anti-GBM glomerulonephritis, as the viral load of the patient was undetectable and he did not present with other active or recent infections that would contraindicate such a procedure. This treatment is based on the premise that the autoantibodies are responsible for the tissular lesion, and the aim is their removal and blockage of their synthesis. Plasmapheresis (4L/day during 14 days) concomitant to the administration of cyclophosphamide (2-3 mg/kg/day) and prednisone (1 mg/kg/day) for three months has been successfully used [2,3,15]. Post-treatment relapse is rare, and in some cases has been related to smoking. In non-treated cases, antibody titers can be detected in the blood for up to one year or more [3]. For those patients progressing to irreversible renal failure, renal transplantation can be performed safely after the antibodies are no longer detectable in the blood. Some researchers consider it wise to wait at least six months after the first post-therapy negative result or at least two years for non-treated patients [3].

When the treatment is initiated with serum creatinine inferior to 600 µmol/L (6.7 mg/dL), 80% to 90% of the patients are maintained without the need for dialysis after one year. When treatment is initiated with the patients already in dialysis or with serum creatinine superior to 600µmol/L, this percentage falls to 0% to 18% [2]. Alternatively, immunoadsorption with protein A has been used in substitution for plasmapheresis [16,17]. Also, mycophenolate mofetil was administered with success to one patient with frequent relapses of lung hemorrhage, utilizing the normal dosage [18].

In our patient, there was no evidence of a short-term response, and as the patient developed leukopenia with the use of cyclophosphamide, after conclusion of the conventional initial treatment, the immunosuppressive drugs were discontinued.

The most intriguing aspect of this case report is the association between anti-GBM glomerulonephritis and HIV infection. Currently, there is sufficient evidence that HIV is etiopathogenetically involved in several autoimmune phenomena [19]. Antibodies against platelets and white blood cells have been demonstrated in patients with AIDS [20]. It has also been demonstrated that T-cells infected by HIV may expose previously occult $CD_4$ epitopes, leading to downregulation of the $CD_4$ molecules, mediated by monoclonal antibodies against $CD_4$ or gp-120 [21]; in addition, there is evidence that an autoimmune response mediated by T-cells is involved in the pathophysiology of HIV infection [21], and that it is likely that IL-6 and IL-10 are involved in the development of malignancy and autoimmunity in AIDS [22].

The association between membranous nephropathy and vasculitis with anti-GBM antibodies favors the hypothesis that GBM damage in these diseases can trigger an autoimmune response against GBM [2]. This hypothesis is also further corroborated by two case reports that describe patients who developed Goodpasture's syndrome after lithotripsy [23,24]. There is also an epidemiological association between exposure

**Figure 1.** Diffuse crescentic glomerulonephritis, accompanied by acute tubular necrosis. Note granular casts in tubular lumens (PAS; 100 x)

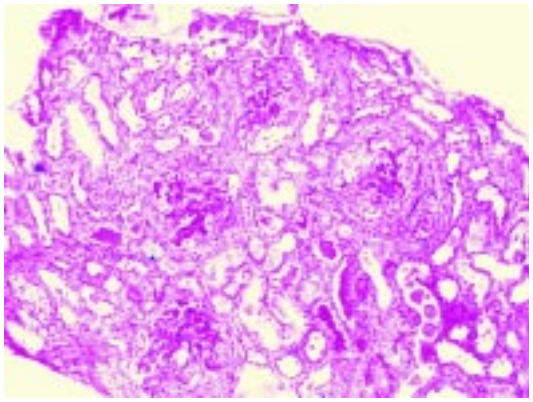
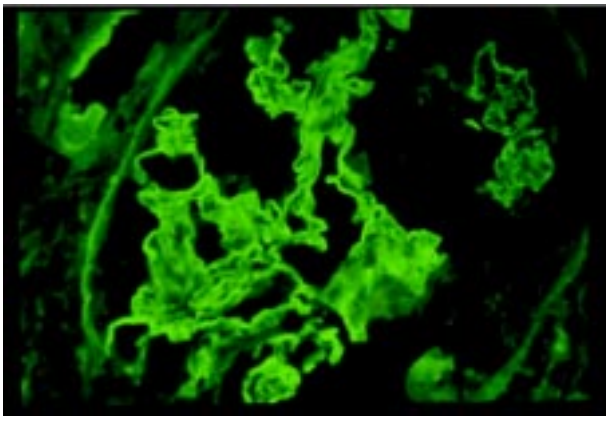


**Figure 3.** Linear immunofluorescence for IgG along the glomerular capillary wall (400x)

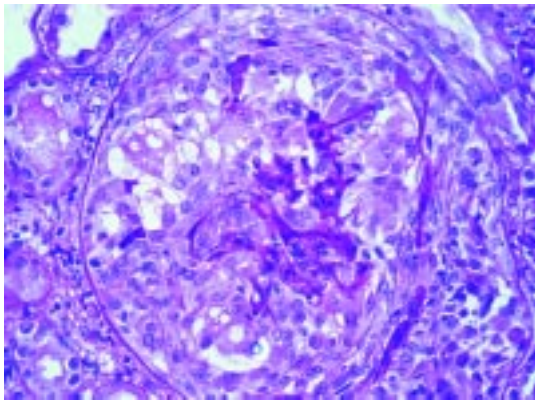


to organic solvents and progressive glomerulonephritis, with the eventual development of Goodpasture's syndrome [2]. The antigen involved is the α3 chain of type IV collagen, the main structural component of the glomerular basement membrane. The antigenic region of the molecule is the 230 amino acid non-collagen domain called NC1, in the carboxyl terminal region [1,2,25].

Calderon et al. [1] detected anti-GBM antibodies, with evidence of anti-GBM glomerulonephritis, in HIV-negative patients with *Pneumocystis carinii* lung infection, and not in HIV-negative patients who carried the pathogen but did not have pneumonia, which suggested that the alveolar lesion caused by the agent is responsible for the development of the autoimmune disease. Moreover, HIV-positive patients with *P. carinii* pneumonia did not present anti-GBM antibodies.

On the other hand, Savige et al. [26] found anti-GBM antibodies in 17% of HIV-positive patients, with a significant correlation between the presence of the antibody and $CD_4$ counts lower than 400/mL. Also, antinuclear antibodies were found in 23% and ANCA in 17% of the HIV-positive subjects. There was no correlation between the presence of antibodies

**Figure 2.** A large cellular crescent with a partially destroyed and compressed capillary tuft (PAS; 400x)



and the development of autoimmune disease. Even with moderate and elevated titers of anti-GBM antibodies in one of the cases, there was no clinical or laboratory evidence of glomerular disease. It is noteworthy that even normal individuals may have increased serum levels of some autoantibodies with no manifestation of disease [27-29].

Our report yields the hypothesis that the immune response in HIV patients may be etiopathogenetically involved in the development of anti-GBM glomerulonephritis. Some findings reinforce the idea that the association described in this case is not casual, such as: crescentic glomerulonephritis is not common in HIV-positive patients [26], anti-GBM glomerulonephritis is rare and anti-GBM antibodies are frequently observed in HIV-positive subjects when compared to the overall population [26].

We conclude that HIV-positive subjects with anti-GBM antibodies deserve special attention concerning the early diagnosis of eventual urinary abnormalities, considering the severity of anti-GBM glomerulonephritis. It is intriguing that anti-GBM glomerulonephritis has not been reported more frequently in HIV-patients, due to the number of these patients with anti-GBM antibodies in their serum and that these antibodies have a recognized pathogenetic role in such glomerulonephritis [26]. Based on our case report and on the elevated frequency of positivity for such antibodies in this group of patients, it is advisable to be aware of a possible association between these two conditions and to promote an active search for anti-GBM antibodies in HIV-positive subjects.

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