BioSCIENCE Case Report
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Anti-glomerular basement membrane disease with exclusive renal impairment

Doença antimembrana basal glomerular com acometimento renal exclusivo

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PALAVRAS-CHAVE: Glomerulonefrite. Biópsia por Agulha. Diálise.

INTRODUCTION

Anti-glomerular basement membrane (anti-GBM) disease is rare and potentially lethal.[1] It has an autoimmune cause of antibodies against antigens in the basement membrane of pulmonary and renal vessels.[2] Thus, it is considered vasculitis of small vessels that can affect both glomerular and pulmonary capillaries3. For cases with concomitant glomerulonephritis and alveolar hemorrhage, in addition to the presence of anti-GBM antibodies, the eponym "Goospasture's disease" is used, in honor of the American pathologist Ernest Goodpasture who described this syndrome in 1919 - at the time attributed to the atypical manifestation of the influenzae virus.[4]

It seems to have a bimodal distribution, affecting young patients between 20 and 30 years of age, predominantly men in the form of lung-kidney syndrome, and in older patients, between 6 and 7 decades, with a predominance in women in its exclusive renal involvement form.[2]

The proposed theme is of great relevance in the area, since it is a "prototype" autoimmune disease with several differential diagnoses, such as: ANCA vasculitis (anti-cytoplasmic neutrophil antibodies) associated (granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis), small vessel vasculitis by immune complexes, (systemic lupus erythematosus, cryoglubulinemia, Henoch Schnlein purpura), mixed connective tissue diseases (systemic sclerosis, dermaromyositis and poliomyositis), antiphospholipid antibody syndrome, infectious diseases, and, finally, primary kidney disease, associated with lung disease, mimicking lung-kidney syndrome.[2] In addition, although rare - estimated incidence of 1-2 cases per million Europeans per year - it is an aggressive autoimmune condition, and therefore of great diagnostic relevance.[5]

This report has the additional objective of reviewing clinical and laboratory alterations of the disease, as well as diagnostic and therapeutic tools.

CASE REPORT

A 74-year-old woman with hypothyroidism and gastroesophageal reflux disease, using levothyroxine 88 mcg and omeprazole 20 mg a day, sought the Emergency Care Unit (UPA) due to lipothymia and hypotension (70 x 40 mmHg). After laboratory tests, glomerular filtration alterations and anemia were identified (urea 97.4 mg/dL; creatinine 3.66 mg/dL; hemoglobin 10.7 g/dL; hematocrit 31.1%; mean corpuscular volume 77.8 fl, with microcytosis +) and referred to a specialized service.

On admission, she denied previous renal alterations (baseline creatinine 0.^{88} mg/dL), as well as other comorbidities, in addition to those mentioned, and presented with normotensive, with no other relevant alterations on physical examination. From medical history, she had only had saphenous vein He denied alcoholism and smoking.

Measures for metabolic control such as hyperkalemia and volume correction were initiated. In view of the acute renal alteration and the finding of microscopic hematuria in partial urine, erythrocyte dysmorphism was investigated, with positive results, thus suspecting glomerulopathy. Due to the exponential worsening of renal function in a few days, with a decline of more than 50% in the glomerular filtration rate, the diagnosis of rapidly progressive glomerulonephritis was suggested, and pulse therapy with methylprednisolone and renal biopsy were performed.

In addition, ultrasonography of the urinary tract was performed, which showed a slight reduction in the thickness of the right kidney parenchyma (95 mm in the longest axis and 9 mm in the parenchymal thickness),

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without other relevant changes; CT scans of the chest, abdomen and pelvis showed no significant changes.

In the laboratory investigation, the patient had negative viral serology (HbsAg; anti-HCV; anti-HIV; VDRL), reactive antinuclear antibody (reactive chromosomal metaphase plaque, almost homogeneous nuclear pattern, titer greater than 1:640), ANCA (antineutrophil cytoplasmic antibodies) P positive, cryoglobulin negative and complements within the normal range. In view of these results, a probable associated ANCA vasculitis, restricted to the kidney, was raised. However, renal biopsy - only available after the patient's discharge - confirmed the diagnosis of anti-GBM disease, with crescent glomerulonephritis in the proliferative/sclerosing phase.

Light microscopy revealed 21 glomeruli, of which 43% were globally sclerotic, with frequent glomeruli compromised by crescent lesions, and 30-40% of the glomeruli visualized associated with fibrosis and interstitial granulomononuclear infiltrate with the coexistence of interstitial edema. It was also observed that blood casts and foamy cells filled the tubules. The immunofluorescence reaction revealed a positive linear pattern of strong intensity, highlighting the IgG in the capillary loops along the glomerular basement membrane, with the association of strong immunostaining of the same pattern for C3, Kappa and Lambda. The other markers IgA, IgM and C1 were negative. Therefore, the findings constituted rapidly progressive crescentic glomerulonephritis, type I (immune-mediated) (Figures 1, 2 and 3)

After 10 days of hospitalization, she required renal replacement therapy, being linked to a hemodialysis service, with referral to the peritoneal dialysis program, for evaluation of subsequent transition. With improvement in laboratory tests and stability of the condition, she was discharged with prednisone 1 mg/kg/day, later suspended with the result of the renal biopsy, but other medications were maintained and she was redirected to outpatient follow-up.

DISCUSSION

The case described here exemplifies the disease with exclusive renal involvement, presenting as rapidly

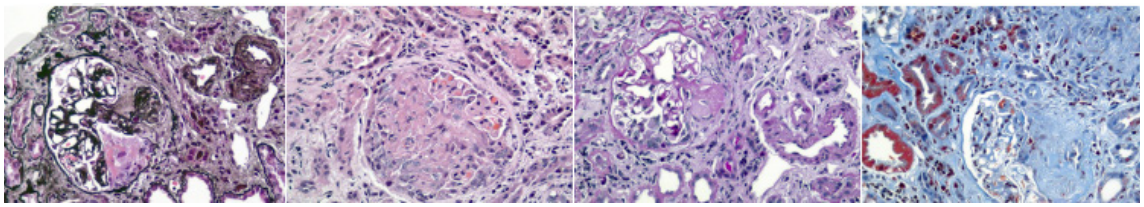

FIGURE 1 — Light microscopy: glomerular compartment

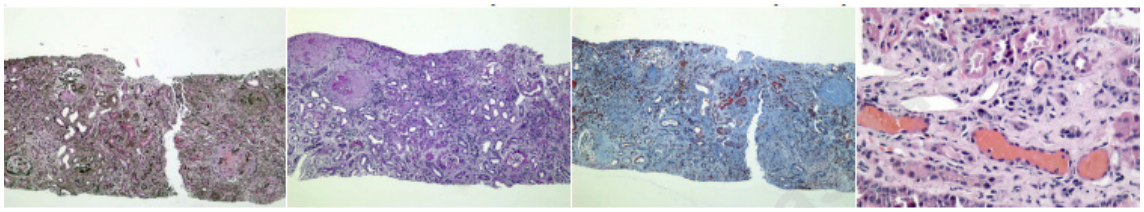

FIGURE 2 — Light microscopy: tubulointerstitial compartment

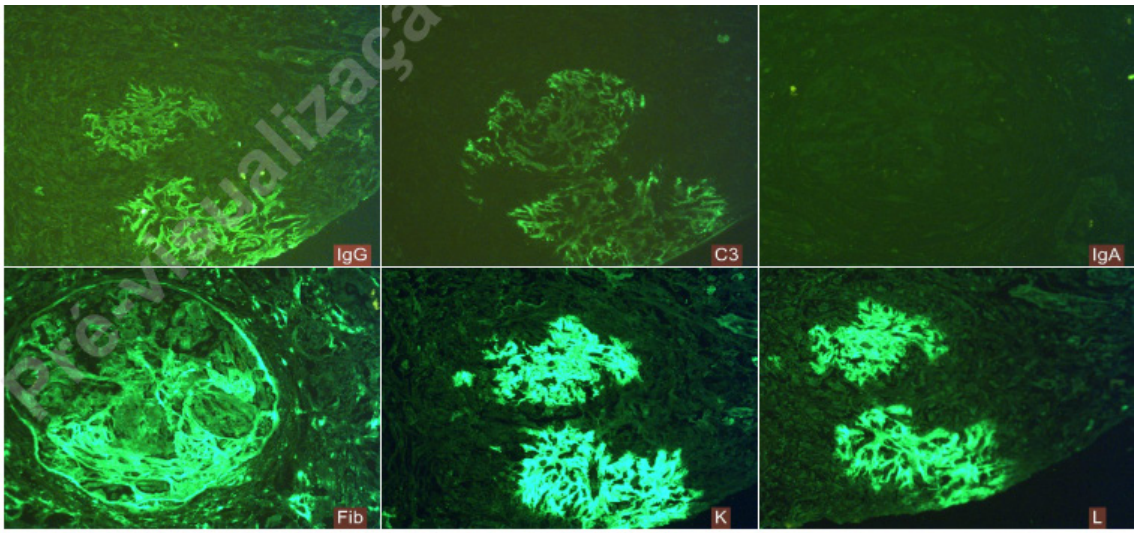

FIGURE 3 — Light microscopy: immunofluorescence

progressive glomerulonephritis (RPGN), defined by a loss of more than 50% of the glomerular filtration rate, in a period of 3 months or even in days to weeks, as in this case.[2]

RPGN is the most severe presentation among glomerulonephritis. The main clinical signs are proteinuria, hematuria, and deterioration of renal function, with frequent extrarenal involvement, such as pulmonary and gastrointestinal symptoms.[4] It is the main presentation of anti-GBM disease, and in 10-15% of them, the presence of anti-GBM antibodies or histology compatible with the disease is identified.[2,5]

The reported clinical manifestation was nonspecific. According to the literature consulted, prodromal signs and symptoms manifest themselves in this way, lasting only a few weeks before the diagnosis is confirmed. Such symptoms consist of malaise, fatigue, weight loss and low fever.[5] It is observed that the presence of fever in anti-GBM disease is infrequent, except in cases in which there is double positivity of antibodies (anti-GBM and ANCA), commonly in the presence of associated infections or recurrence of the disease.[2] Some patients, however, as in the present case, do not present any symptoms until they evolve with complete renal failure.[2,4]

In approximately half of the cases of anti-GBM, the alveolar hemorrhage progresses in conjunction with glomerulonephritis and in the remaining half with exclusive renal involvement, and only 5% with only pulmonary presentation.[2,4,5]

As an autoimmune condition, anti-GBM has multiple triggering factors for its manifestation, as well as susceptibility to specific alleles added to environmental, genetic, seasonal and infectious interferences.[2] Although the pathogenesis at the molecular level is well known, the triggers of the autoimmune response remain poorly understood. Environmental interference is suspected; however, due to its rarity, there are few epidemiological data to define this correlation.[1] It is suggested that other environmental triggers such as inhalation of irritative gases (such as hydrocarbon or related to smoking) alter the permeability of the capillary membrane, predisposing to alveolar hemorrhage in those individuals who have anti-GBM antibodies. Such irritants may also play a role in the triggering of the immune response, releasing or modifying pathogenic self-antigens from the basement membrane.[2]

The diagnosis of anti-GBM disease consists of the presence of anti-GBM antibodies in conjunction with renal and/or pulmonary disease. These antibodies can be detected by direct immunofluorescence in a kidney biopsy sample or by detection in the bloodstream by enzyme-linked immunosorbent tests. In this case, the presence of antibodies by renal biopsy was used as diagnostic criteria, in addition to the clinical presentation with renal involvement.[1]

As evidenced in the analysis of the renal fragment by immunofluorescence, the typical diagnostic finding consists of a linear pattern of IgG deposition along the basement membrane, commonly accompanied by complement deposition (C3) and rarely with a linear pattern of IgA and IgM. This result can also be detected in patients with diabetic nephropathy or kidney transplants without signs of glomerulonephritis, as well as other staining patterns can also be detected in both mild and severe cases.[2] This method has high sensitivity for antibody detection and is the gold standard for diagnosis. However, it can be negative in cases where there is a severe inflammatory state with structural alteration.[2]

The histological pattern of the sample typically consists of necrotizing and crescentic glomerulonephritis, on light microscopy, without mesangial hypercellularity, endocapillary or features of microangiopathy.[2,4] On the other hand, in the analysis by antibodies circulating in the bloodstream, although they have high sensitivity and specificity (>95% and >91%), it is estimated that 5-10% of patients with anti-GBM demonstrable in renal biopsy have negative serum tests.[1,2]

Thus, renal biopsy is recommended, even with serum anti-GBM positivity, because the linear deposition of immunoglobulins along the basement membrane in the context of crescent glomerulonephritis is also diagnostic. In addition, it can provide important information about the activity and chronicity of kidney damage that can help guide therapy.[1]

It is important that serological tests for the detection of anti-GBM are available in hospital centers and that they have their results within 24 h, especially in cases of RPGN that have contraindications for biopsy. With this tool, which is widely available, there would be greater agility in the choice of therapy, before the need for renal replacement therapy, possibly ensuring a better outcome.[2,5]

The treatment proposed in this case initially consisted of high doses of corticosteroids, since the diagnosis of associated ANCA vasculitis was considered. The standard for anti-GBM disease, however, consists of plasmapheresis in conjunction with corticosteroids and cyclophosphamide, for rapid removal of pathogenic autoantibodies and reduction and inhibition of the inflammatory process. This association has been described since 1976 and remains recommended by the "Kidney Disease Improving Global Outcomes guideline for treating anti-GBM GN".[2]

In the case of the patient in question, corticosteroid therapy was maintained until reassessment at the outpatient follow-up, when it was withdrawn, considering the non-extrarenal involvement and the severity of the kidney injury. The duration of immunosuppression maintenance is not well defined. It is suggested that therapy be maintained for a few months, with 2-3 weeks of plasmapheresis, approximately 3 months of cyclophosphamide and corticosteroids, and finally 6-9 months of corticosteroid therapy alone. There are also some reports of azathioprine as a maintenance dose.[1,5] It is noted that treatment with corticosteroids and cliclophosphamide has a favorable effect on survival, although it does not impact renal preservation.[5]

In patients with active lung injury, plasmapheresis is indicated. Clinical status and serum levels of anti-GBM should be noted and are no longer necessary if there is a drop in serum levels of the antibody. However, it should be continued if active lung disease persists, or if antibody titers do not reduce.[2,4,5] It is estimated that the severity of renal impairment at presentation, as well as the proportion of affected glomeruli with crescents and oliguria, are associated with unfavorable renal outcome.[2,5]

Thus, there is a consensus in the literature on the importance of early diagnosis so that adequate treatment can be instituted, especially in cases of alveolar hemorrhage or before the onset of complete renal failure, given the more dramatic outcome in these cases, especially when associated.[1]

However, the benefit of treatment in patients with advanced renal disease without alveolar hemorrhage remains controversial. In general, patients with kidney-limited disease, with >80% increasing on biopsy, rarely benefit from therapy.[1,5] For cases in which there is alveolar hemorrhage, regardless of renal status, treatment is indicated, as well as for all cases with renal involvement who do not immediately require hemodialysis.[5]

Plasmapheresis and immunosuppressive therapy are indicated for a few weeks in those with acute illness with unpredictable irreversible injury, and in young people, as they tolerate more aggressive immunosuppressive therapies better.[2,4,5]

In the case of this patient, it was possible to perceive the ANCA positivity, which at a certain point, brought the associated ANCA vasculitis as a differential diagnosis; however, there are several reports in the literature of the presence of double antibody positivity, anti-GBM and ANCA, and this association is much more frequent than expected. There is a greater trend towards renal recovery from dialysis after treatment, with intermediate renal survival.[2]

Anti-GBM does not have its pathogenesis completely defined, the association with ANCA positivity and its variations in clinical presentation can challenge clinical diagnosis. The role of clinical suspicion associated with renal biopsy in the management of these patients is important.

Authors' contributions

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Writing (proofreading and editing): Laura Garcia de Andrade Oliveira, João Luis dos Santos Carneiro

REFERENCES

1. Alchi B, Griffiths M, Sivalingam M, Gallagher H, Sinha S. Predictors of renal and patient outcomes in anti-GBM disease: clinicopathologic analysis of a two-centre cohort. Nephrol Dial Transplant. 2015;30(5):814-21. Doi: 10.1093/ndt/gfu399
2. Gulati K, McAdoo SP. Anti–Glomerular Basement Membrane Disease. Rheum Dis Clin North Am. 2018;44(4):651-73. Doi: 10.1016/j.rdc.2018.06.011
3. Jennette JC. Overview of the 2012 revised International Chapel Hill Consensus Conference nomenclature of vasculitides. Clin Exp Nephrol. 2013;17(5):603-6. Doi: Overview of the 2012 revised International Chapel Hill Consensus Conference nomenclature of vasculitides
4. McAdoo SP, Pusey CD. Anti-Glomerular Basement Membrane Disease. Clin J Am Soc Nephrol. 2017;12(7):1162-72. Doi: 10.2215/CJN.01380217
5. Van Daalen EE, Jennette JC, McAdoo SP, Tam FWK, Pusey CD, Alba MA, et al. Predicting Outcome in Patients with Anti-GBM Glomerulonephritis. Clin J Am Soc Nephrol. 2017;13(1):63-72. Doi: 10.2215/CJN.04290417