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Case Report

Goodpasture Syndrome with Neurological Condition Associated with anti-MBG Ab, Negative ANCA: Case Report

Paola Alcalá Ramos[1*], Gabriela Alcalá Ramos[2], M. Isabel Alcalá Ramos[3]

[1]Paola Alcalá Ramos Resident Physician of Internal Medicine at ISSSTE-HR Presidente Juárez
[2]Gabriela Alcalá Ramos is Resident Physician of Internal Medicine at IMSS HGZ 47 Vicente Guerrero
[3]María Isabel Alcalá Ramos Resident Physician at ISSSTE-HG Tacuba

***Corresponding Author:** Paola Alcalá Ramos
Paola Alcalá Ramos Resident Physician of Internal Medicine at ISSSTE-HR Presidente Juárez

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Abstract: Goodpasture syndrome is a rare immunologically based clinical entity that is characterized by rapidly progressive glomerulonephritis, diffuse pulmonary hemorrhage, and the presence of circulating autoantibodies against the glomerular basement membrane (GBM). Concomitant central nervous system (CNS) manifestations are an unusual presentation of GSP in the absence of ANCA. We present a case of atypical course of the disease in a 48-year-old female patient who started with the presence of hemoptoic sputums and manifestations of uremic syndrome in the presence of high titres of glomerular basement anti membrane antibodies (Ac-anti-MBG) and negative ANCA, with a report of diffuse active extracapillary proliferative glomerulonephritis biopsy, of the pauciimmune type. After immunosuppressive treatment and plasmapheresis, the patient presented decreased anti-MBG Ab titres, as well as improvement of symptoms, however without recovery of renal function on hemodialysis, after 2 months he presents clonic-tonic seizures crisis, we conclude that PGS with neurological involvement is extremely rare, especially with negative ANCAs.

Keywords: Goodpasture's syndrome, rapidly progressive Glomerulonephritis, glomerular basement membrane antibodies.

INTRODUCTION

Rapidly progressive glomerulonephritis (RPGN) comprises a series of disorders of varied etiology and pathogenesis, which present clinically with a syndrome characterized by a rapid loss of renal function (usually more than 50% of the baseline glomerular filtration rate in a period not exceeding to three months) and with findings in urine characteristic of glomerulonephritis (hematuria and, frequently, proteinuria of glomerular origin) [1].

This clinical diagnosis requires the performance of a renal biopsy (PRB) that will confirm, under a light microscope, the presence of an extensive proliferation of cells in the Bowman space of the glomeruli (half-moons in, usually, more than 50% of them), which configures the anatomopathological diagnosis of diffuse extracapillary proliferative glomerulonephritis (DPGN) [2].

It is almost invariably associated with poor prognosis for renal and patient survival. It must be diagnosed and treated quickly, regardless of its pathophysiology. This is usually established around the data of the clinical presentation, the laboratory and mainly the immunofluorescence analysis of the PRB sample [3].

RAPIDLY PROGRESSIVE TYPES OF GLOMERULONEPHRITIS

Immunohistochemistry usually refers to five types of patterns in this entity [4]:

1) Type I RPGNs, comprising anti-Glomerular Basement Membrane (anti-GBM) antibody disease, with or without alveolar hemorrhage.

2) GNRP type II, which refers to a large group of pathologies that have in common the deposition of immunocomplexes in the affected organ (some severe forms of luteal nephropathy class IV, IgA vasculitis, cryoglobulinic glomerulonephritis with crescents, postinfectious glomerulopathies with GPED, etc.).
3) Type III GNRPs, of a pauciimmune nature (in relation to the little or no expression in the immunohistochemistry of deposition of antibodies directed against some antigen, typical of the glomerulus, or deposited from the circulation). It is estimated that at least 80% of these are pathogenically associated with anti-neutrophil cytoplasm antibodies (ANCA).
4) Type IV RPGNs, type I and type III combination.
5) Type V RPGNs, pure pauciimmune without the presence of positive ANCA.

We present the case of a 48-year-old patient with diffuse active extracapillary proliferative glomerulonephritis of the pauciimmune type, accompanied by hemoptotic sputum and generalized tonic-clonic seizures, in the presence of elevated anti-MBG Ab and negative ANCA titers.

CASE REPORT

A 48-year-old woman with no significant background. She did not use any other regular medication, nor did she take any medication temporarily before the illness. Onset of illness in July 2020 with general malaise, vertigo, deterioration of general condition, later headache, edema of pelvic limbs and manifestations of uremic syndrome were added. Assessed by a private nephrologist under study protocol by MNG of rapidly progressive behaviour, who requests immunological studies with negative results. Haemodialysis was started on 10.07.2020. With a kidney biopsy report on 19.08.20 diffuse active extra capillary glomerulonephritis of the paciimmune type, the data found characteristic and compatible with vasculitis, so that the ANCAS were repeated with a negative report again, however, positive anti-MBG Ab. Management was initiated with immunosuppression with glucocorticoids (prednisone 50mg PO every 24 hours) and rituximab 500mg in two doses (last 7.08.20). Therefore, according to histopathology, diffuse active extra capillary proliferative glomerulonephritis was suggested, of the pauciimmune type, with segmental fibrinoid necrotizing lesions. Immunofluorescence for IgG, IgA, IgM were negative. And the glomerular basement membrane Ab were positive, a diagnosis of pauciimmune extra capillary glomerulonephritis associated with anti-MBG Ab was established.

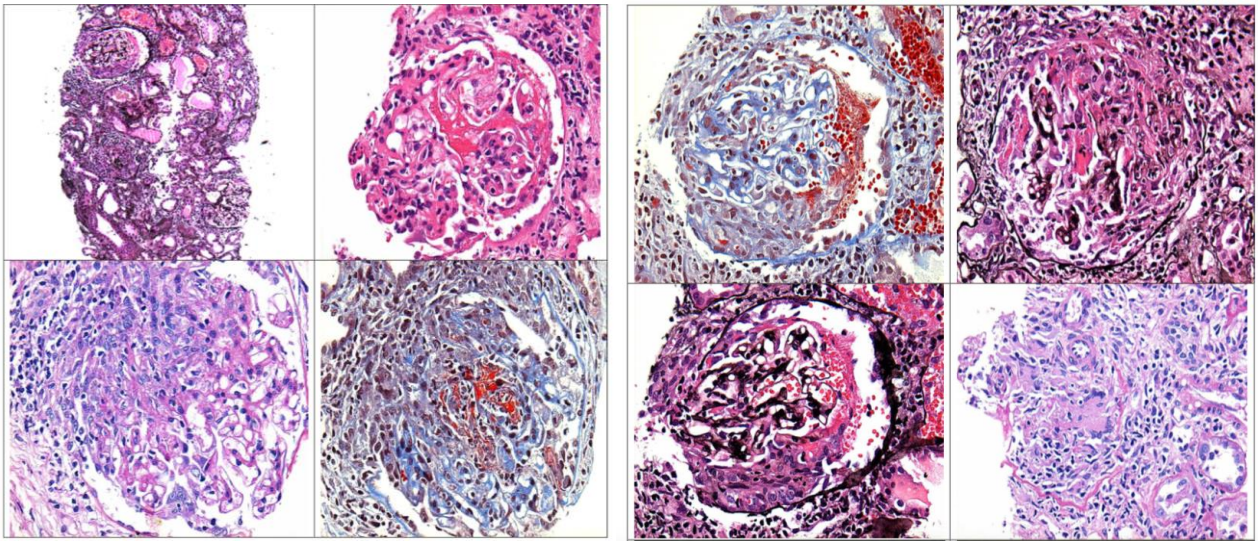

Figure 1: A light microscopy study shows a fragment of renal parenchyma (predominantly cortex) that has eight glomeruli per section in total, three of these (37.5% of the total glomeruli in the sample) have segmental sclerosing lesions of scar appearance, which form synechiae between the hair tangles and Bowman's capsules (secondary). In six glomeruli (75%), active extra capillary proliferative lesions (cell moons) can be seen, with karyoresis and areas of fibrinoid necrosis, which segment the hair tangles and cause disruption of Bowman's capsules, with periglomerular granulomatous inflammatory reaction

Admission to hospital on 14.08.20. On clinical examination, the patient had an endomorphic constitution with a body mass index BMI of 28.1, afebrile, palsy of integuments, with bilateral peripheral edema. He developed scarce hemoptysis on 17.08.20, breathing difficulty SO2 85% in ambient air, so he required supplementary oxygen. Computed tomography (CT) of the thorax revealed opacities in both lungs images in stripped glass, mainly with bilateral perihilar distribution suggestive of alveolar hemorrhage.

Therefore, treatment with methylprednisolone 1 gram through IV every 24 hours for 3 days begins on 17.08.20. On 18.08.20 anti-glomerular basement membrane Ab 661.60 U/ml.

Because of data suggesting active bronchoalveolar hemorrhage with decreased hematocrit, cyclophosphamide at a dose of 1gr/m2 on 21.08.20 was started, she received 1st dose cyclophosphamide in addition to 5 plasmapheresis sessions on alternate days.

Controls of anti-GBM antibodies were taken after the start of plasmapheresis and chemotherapy, obtaining the following: 01.09.20 Anti-glomerular basement membrane Ac 109.52 U/ml.

After immunosuppressive treatment associated with plasmapheresis, the patient presented with decreased control antibody titers from 15.09.20 Anti glomerular basement membrane Ab 23.52 U/ml, as well as improvement of symptoms altho rugh without recovery of renal function, remaining on hemodialysis program andeceived on an outpatient basis on 22.09.20 2nd dose cyclophosphamide 1gr IV + 800 mg mesna.

SUBSEQUENT EVOLUTION

After 2 months, on 20.10.20 he presents a clonic tonic seizure, assessed by neurology on 20.10.20 who, according to history and simple and contrasted CT of the skull in which only a left temporal granuloma was observed, establishes a diagnosis of probable small vessel cerebral vasculitis, not ANCA due to Goodpasture syndrome. So he entered internal medicine on 22.10.20, antibody controls 23.10.21 anti MBG antibodies 8.06 U/mL and received 3rd cycle of cyclophosphamide 1250mg + 800mg of mesna.

DISCUSSION

The typical presentation is that of a renopulmonary syndrome, that is, the combination of renal and pulmonary failure. However, many other types of presentations have been described [10]. As in this case, multisystem involvement of vasculitis was observed in a 48-year-old woman with Goodpasture's syndrome and concomitant seizures.

PGS with neurological involvement is extremely rare, especially with negative ANCA [9]. Identification of ANCA in patients with anti-glomerular basement membrane disease may define a subset of these patients. It is unclear why neutrophil anti-cytoplasmic antibodies develop in glomerular basement membrane disease; some authors suggest polyclonal activation as a possible mechanism [9]. The pathogenesis of vasculitis in these cases has been observed to correlate closely with ANCA titre.

Although both perinuclear and cytoplasmic Anca have been described in patients with glomerular anti-basement membrane disease, no cross-reactivity between ANCA and anti-MBG antibodies has been reported. Hellmark *et al*., [5] reported no differences in the specificity of anti-GBM antibodies with or without ANCA. The anti-GBM antibody in both groups was found to react primarily with the NC1 domain of the alpha-3 chains of type IV collagen, with no cross-reactivity between ANCA and anti-MBG antibodies [6]. This supports the idea that perhaps lung and glomerular tissue damaged as a result of exposure to Anca may lead to the development of anti-MBG antibodies in the samepatient [5].

Negative PRS ANCA is a rare entity. Approximately 80-90% of PRS patients have one or more autoantibodies. Many patients (20-35%) with anti-GBM antibodies also have anti-neutrophil cytoplasm antibodies (ANCA), mostly with specificity for myeloperoxidase (MPO-ANCA) [10]. In addition, recent studies have suggested that the pathogenesis of "double seropositive" patients, i.e., those with anti-GBM disease and anti-neutrophil cytoplasm antibody (ANCA) - associated vasculitis, could be explained by the presence of intermolecular epitopes [11]. Uncategorized PRS pathogenesis with negative serology for several antibodies, as in this case, is extremely rare.

Patients presenting with ANCA-negative vasculitis with pauciimmune immune glomerulonephritis may have significant systemic involvement. Early diagnosis and early immunosuppressive therapy in the form of corticosteroids and cyclophosphamide significantly improves prognosis [4].

The report of cases that developed CNS vasculitis with negative ANCA in the presence of elevated a-GBM Ab titres is uncommon, however it is reported as atypical Goodpasture Syndrome [6-9]. In this case, no diagnosis was obtained through a brain biopsy, since it is the gold standard, however, diagnosis was made by clinical picture and imaging studies. Normal brain CT findings do not exclude the possibility of small vessel cerebral vasculitis, as in thiscase [9].

Renal transplantation in case of CNS affection, a waiting time of at least 6 months has been suggested and performed when anti-MBG Ab titres are undetectable, presenting a good subsequent clinical evolution and without recurrence data of renal disease [9]. A more detailed view of the pathogenesis about the role that anti-MBG antibodies

could play in the pathogenesis of CNS vasculitis, will confer greater viability to the prospect of developing effective immunotherapies in thefuture [11].

Finally, we conclude that PGS with neurological involvement is extremely rare, especially with negative ANCAS.

Ethical Responsibilities

Protection of people and animals: The authors declare that no experiments have been carried out on humans or animals for this research.

Data confidentiality: The authors declare that they have followed their workplace's protocols regarding the publication of patient data.

Right to privacy and informed consent: The authors have obtained informed consent from the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

Use of artificial intelligence to generate texts: The authors declare that they have not used any type of generative artificial intelligence in the writing of this manuscript or for the creation of figures, graphs, tables or their corresponding captions or legends.

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