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Pneumorenal Syndrome Complicating ANCA-Negative Pauci-Immune Vasculitis Associated with Atypical Mycobacteriosis: Case Report

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Abstract **Case Report**

Among the forms of pneumorenal syndrome (PRS), one of the most urgent is characterized by the combination of diffuse alveolar hemorrhage and rapidly progressive glomerulonephritis (RPGN). In 90% of cases, it is the manifestation of an autoimmune disease, such as pauci-immune vasculitis with anti-neutrophil cytoplasmic antibodies (ANCA) or Goodpasture's disease with the presence of antibodies directed against the basement membrane of the glomerular and alveolar capillaries (anti-GBM). These antibodies are absent in approximately 10% of cases with histological confirmation in the context of rare clinical situations. We report a case of a 66-year-old patient, with a history of alcoholism and active smoking, who was admitted to the hospital for respiratory distress with hemoptysis. The admission assessment showed severe renal failure requiring hemodialysis upon admission. ANCA and anti-GBM, as well as all other autoantibodies were negative. A renal biopsy revealed pauci-immune extra-capillary glomerulonephritis with the majority of chronic lesions. The orientation of the diagnostic approach in search of other causes of pauci-immune vasculitis with negative antibodies has been initiated. He was treated with glucocorticoids in combination with cyclophosphamide. The initial evolution was marked by the improvement of respiratory symptoms and a less considerable recovery of renal function. PRS can develop without the presence of ANCA or other autoantibodies. The diagnosis is then made by histology. Renal damage, such as extra-capillary glomerulonephritis (GN), is more severe and has a very poor prognosis with a high risk of mortality. The absence of ANCA should never delay diagnosis and treatment.

Keywords: Pauci-immune vasculitis, alveolar hemorrhage, glomerulonephritis.

INTRODUCTION

PRS is a rare diagnostic and therapeutic emergency. This is a heterogeneous group of multi-system disorders wherein renal and pulmonary disorders predominate. Pulmonary symptoms can range from asymptomatic alveolar infiltrate to alveolar hemorrhages with episodes of hemoptysis, cough and dyspnea. Renal manifestations are necrotizing glomerulonephritis with crescents, active urinary sediment with hematuria, proteinuria and renal failure. One form of PRS combines diffuse alveolar hemorrhage and rapidly progressive glomerulonephritis [1, 2]. The etiologies are dominated by pauci-immune vasculitis associated with anti-neutrophil cytoplasmic antibodies (ANCA) (70%) and anti-glomerular basement membrane antibody disease (anti-GBM) (20%) [3]. In certain cases of pauci-immune vasculitis, ANCAs are not found. This entity remains poorly understood, with different masks at the time of manifestation of vasculitis, a source of nosological ambiguity.

The absence of ANCA should not delay diagnosis and treatment, because any delay is fraught with vital and functional damage with pulmonary and renal after-effects [4].

We report the case of a patient who showed rapidly progressive glomerulonephritis with extracapillary proliferation lesions of the pauci-immune vasculitis type, in a context of negative ANCA with pulmonary manifestations during atypical mycobacteriosis caused by Mycobacterium avium

complex. Our aim is to understand the pathogenic mechanism involved and to remind clinicians to think about this rare clinical entity, even when the immunological assessment is negative.

Presentation of the case

A 66-year-old- Caribbean man was transferred to the Department of Nephrology after his stay in the ICU where he was admitted for respiratory distress associated with hemoptysis lasting for 2 months in a context of deterioration in general condition. His history was marked by smoking and active alcoholism. The initial clinical examination noted dyspnea with desaturation, bilateral crackles on pulmonary auscultation, with edema of the lower limbs. The biological assessment found microcytic anemia at 8g/dl, an impure nephrotic syndrome made up of proteinuria at 8g/g with hypoalbuminemia at 20g/l, renal failure at 837µmol/l oligo-anuric requiring hemodialysis immediately and microscopic hematuria. The serologies were negative. The immunological assessment was unremarkable with ANCA (anti myeloperoxidase (anti-MPO) or anti proteinase 3 (anti-PR3)) and anti-MBG negative. Protein electrophoresis was without significant abnormalities and the complement was not consumed. A renal biopsy punction was performed revealing extra-capillary glomerulonephritis of the pauci-immune vasculitis type with the majority of chronic fibrous crescent lesions and extensive interstitial fibrosis (60-70%). Immunofluorescence (IF) was negative.

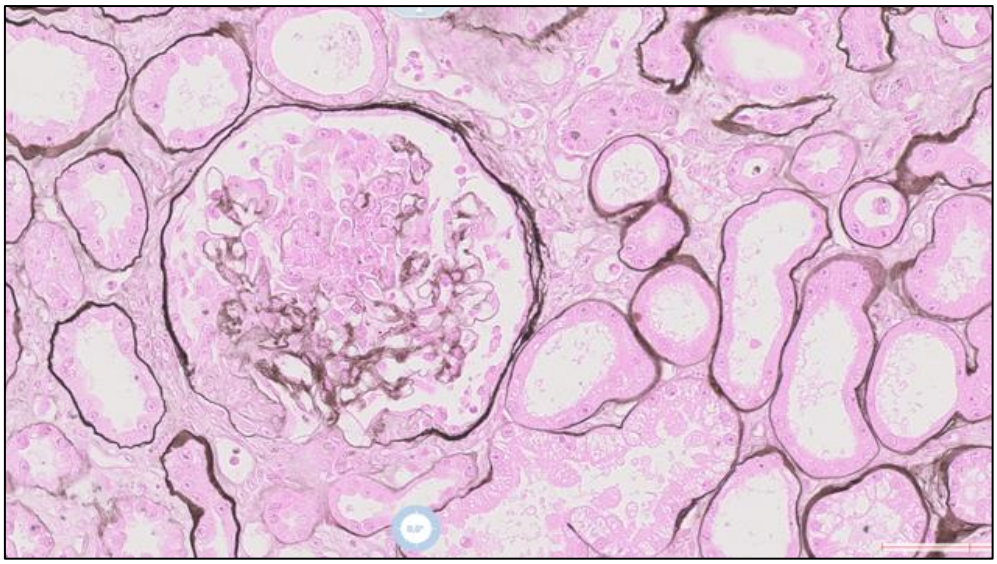

Figure 1: Active fibrinoid necrosis lesion on a glomerulus associated with extracapillary cell proliferation

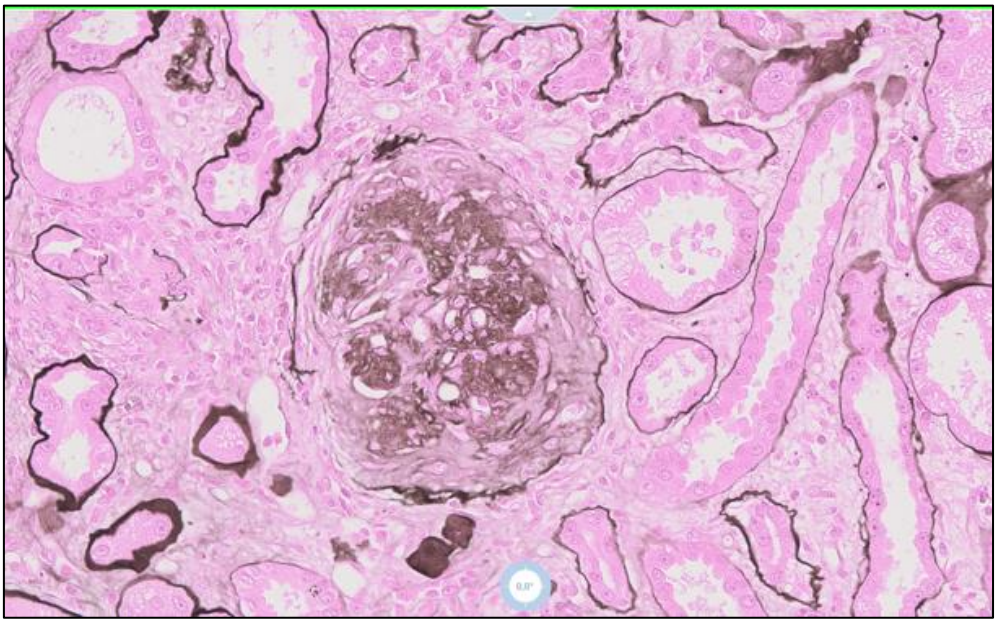

Figure 2: Fibrous crescent lesions found on the 1/3 of the glomeruli

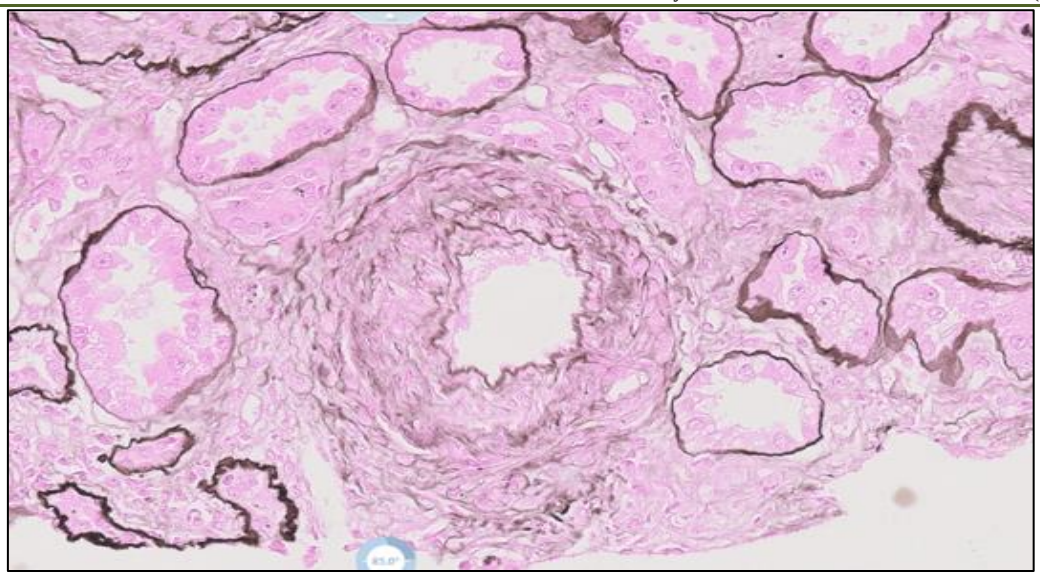

Figure 3: Severe arteriosclerotic lesions

An injected chest CT scan was performed revealing parenchymal lesions, caves with alveolar condensation affecting the right pulmonary field. A fibroscopy with bronchoalveolar washing did not reveal any siderophages, but microbiology confirmed the presence of Mycobacterium avium complex in 3 samples.

An eso-gastro-duodenal endoscopy performed in the presence of an episode of upper digestive hemorrhage noted grade D esophagitis with an antral ulcer and ulcero-necrotic bulbo-duodenitis (placed on a proton pump inhibitor), without vasculitis lesions found at histology.

Therapeutic management required intubation and sedation with mechanical ventilation complicated by intensive care neuropathy, with good progress after tracheotomy with physiotherapy. He benefited from extra-renal purification sessions upon his admission due to oligo-anuric renal insufficiency. For the treatment of pauci-immune vasculitis, he was given a high-dose intravenous corticosteroid therapy for 3 days, continued it orally, and received the first dose of cyclophosphamide. An antibiotic therapy based on Clarithromycin, Levofloxacin, Ethambutol and Rifampicin was introduced for the treatment of mycobacteriosis. Besides, he received a blood transfusion 3 times (6 packed red cells).

The initial evolution was favorable on the respiratory level allowing the cessation of sedation and mechanical ventilation with, on the renal level, resumption of diuresis with partial recovery of renal function achieving a plateau around 500µmol/l of creatinine, allowing temporary weaning from hemodialysis resumed in Nephrology.

Subsequently, his general condition deteriorated increasingly with severe malnutrition. He had mood disorders with sometimes care refusal (refusal of magnetic resonance imaging as part of the vasculitis assessment, sometimes refusal of hemodialysis). Then other complications set in. He developed thrombosis of the left basilic vein with difficult anticoagulation given the context of the hemorrhages. Sepsis with urinary origin and a pulmonary infection with Covid-19 occurred, worsening the clinical process with resumption of respiratory distress. Given the patient's fragility related to his immunity, immunosuppression was stopped. The patient died after two months of hospitalization.

DISCUSSION

Pneumorenal syndrome during pauci-immune vasculitis with negative ANCA is a rare entity because 80-90% of patients with pneumorenal syndrome show one or more autoantibodies [5]. The particularity of our case is the presence of extracapillary glomerulonephritis of the pauci-immune type in the absence of ANCA, or other autoantibodies, making the diagnosis and its classification difficult.

Since its first description by Goodpasture in 1919 [6], pneumorenal syndrome is often reported in contexts of pauci-immune vasculitis with positive ANCA as in microscopic polyangiitis and Wegener's granulomatosis, or with the presence of anti-GBM) [7]. Other etiologies such as systemic lupus, anti-phospholipid antibody syndrome, cryoglobulinemia, Henoch-Schönlein purpura, rheumatoid arthritis, mixed connective tissue disease and certain medications (antithyroid drugs, immune checkpoint inhibitors) are known as possible causes of pneumorenal syndrome. ANCAs are often positive and atypical (10-90%), that is,other than anti-MPO or anti-PR3, which may be anti-elastase antibodies [7–9]. However, in 10% of pauci-

immune vasculitis, as it is the case for our patient, ANCAs are not found [8,10]. Histology is then essential to support the diagnosis. The characteristic renal histological lesion common to all etiologies of PRS is extracapillary glomerulonephritis [1].

The prevalence and severity of manifestations of ANCA-negative pauci-immune vasculitis, compared to those of ANCA-positive pauci-immune vasculitis, are reported differently depending on authors. Chen *et al*., in 2007, in a series comparing 28 patients with pauci-immune glomerulonephritis with negative ANCA and 57 patients with pauci-immune glomerulonephritis with positive ANCA, found that the prevalence of clinical manifestations (fever, weight loss, arthralgia, pulmonary, gastro -intestinal, etc.) was lower in ANCA negative patients. On the other hand, on the renal level, ANCA-negative patients had higher proteinuria and a higher prevalence of nephrotic syndrome, with more severe renal histological lesions than in ANCA-positive patients [11].

These differences in extra-renal and renal histological manifestations were not objectified by Villacorta et al. in their series of 114 patients. However, all these authors agree that proteinuria was higher in patients with ANCA negative [12]. Our patient also had massive nephrotic grade proteinuria as reported in cases of ANCA-negative vasculitis, while its extra-renal manifestations resembled those of patients with ANCA-associated vasculitis.

The pathogenesis leading to the occurrence of pauci-immune glomerulonephritis in the absence of ANCA is unclear. In pauci-immune vasculitis associated with ANCA, polynuclear cells (PN), a real hub of pathophysiology, are activated by ANCA by different mechanisms leading to apoptosis of PN and endothelial cells. According to the literature, PN could also play a major role in the mechanism of occurrence of pauci-immune glomerulonephritis with negative ANCA. These PNs would be activated by other types of unidentified autoantibodies or other cell-mediated (T cell-dependent) mechanisms. This is evidenced by the presence of PN in the lesions during pauci-immune vasculitis, independently of the presence or absence of ANCA [13, 14]. As far as our patient is concerned, there was doubt about an infectious cause of pauci-immune glomerulonephritis, given the context of atypical mycobacteriosis. But, the absence of deposit at the IF was not in favor of a GN secondary to the infection, thus supporting the diagnosis of a pauci-immune vasculitis linked to another immune mechanism which has not been elucidated. There is also no evidence of alveolar hemorrhage in the absence of siderophages, which may be absent if BAW is performed within 72 hours of the start of hemorrhage [15].

The standard treatment of pauci-immune vasculitis is based on the combination of high-dose intravenous glucocorticoids for a few days, then taken orally in rapidly decreasing doses, and cyclophosphamide [16]. This combination of glucocorticoid and cyclophosphamide was considered as the "gold standard" until 2010, the year when rituximab demonstrated its non-inferiority [17]. Shah *et al*., in a series of patients suffering from pauci-immune vasculitis with severe renal damage, with and without ANCA, had demonstrated that the remission rate was also satisfactory if the patients were treated with glucocorticoids and Rituximab without cyclophosphamide [18]. A few years before, the RITUXVAS study had validated the induction of remission by Rituximab in case of pauci-immune vasculitis with severe renal damage, but without finding any superiority to cyclophosphamide [19]. Plasma exchanges in combination with glucocorticoids and cyclophosphamide in ANCA-associated vasculitis with severe renal damage increase the rate of recovery of renal function according to the MEPEX study [20], but their interest remains to be discussed according to other literature [21]. Concerning our patient, plasma exchanges were not introduced since ANCAs were negative.

The fact that there was a positive evolution on the respiratory level, with partial recovery of renal function, initially after the introduction of corticosteroid therapy and immunosuppression, this is in favor of the involvement of an immune mechanism in the occurrence of vasculitis in our patient, although it has not been possible to clarify it. Further studies are therefore necessary.

CONCLUSION

Pneumorenal syndrome often occurs in clinical contexts with the presence of autoantibodies, notably pauci-immune vasculitis associated with ANCA and anti-GBM disease. However, it can occur without ANCA or other autoantibodies being found during seroimmunological explorations. Renal damage is therefore more severe and has a very poor short and long term prognosis, with a high risk of morbidity and mortality. The absence of ANCA should therefore never delay the diagnosis and treatment. Renal biopsy is then enough to provide histological proof of the disease.

Interest-Related Conflict: No one signaled.

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