María Carmen Prados Soler, et al., J Nephrol Renal Ther 2023, 9: 075
DOI: 10.24966/NRT-7313/100075

HSOA Journal of Nephrology & Renal Therapy

Case Report

Relapse of P-ANCA Positive Vasculitis with Pulmonary Hemorrhage in Hemodialysis Patient. Therapeutic Challenge

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Abstract

ANCA-Associated Vasculitis (AAV) is a multisystem small vessel disease with a high rate of morbidity (including renal failure and pulmonary involvement) and mortality. Relapses in the course of p-ANCA vasculitis in dialysis patients are rare. We review the case of a patient diagnosed with p-ANCA vasculitis who developed a relapse with reno-pulmonary syndrome 15 months after restarting hemodialysis (HD) replacement therapy. Treatment of VAA requires induction immunosuppression with plasmapheresis, corticosteroids, cyclophosphamide and/or rituximab and maintenance with glucocorticoids and rituximab. The use of high-dose immunosuppression is necessary for disease control, but may contribute to patient mortality through severe infections, hematological toxicity, osteopenia and increased risk of malignancy. The challenge of vasculitis management is to balance the risk of treatment toxicity with the risk of vasculitis relapse. Vasculitis with renal involvement and subsequent relapse on dialysis, the usefulness of ANCA titles in predicting such relapses and treatment options are discussed.

Keywords: Dialysis; p-ANCA; Pulmonary hemorrhage; Vasculitis

Introduction

AAV are rare systemic autoimmune diseases, very heterogeneous and polymorphic in their presentation, characterized by being associated with the presence of ANCAs although these are not always present. They are potentially serious diseases with a high morbidity and mortality without treatment, and with the possibility of relapse [1]. AAV involves the vascular wall of small vessels, where fibrinoid necrosis is observed, with obliteration of the lumen, with little or no immunocomplex deposition. The AAV group includes three distinct entities according to their clinical phenotype: Microscopic Polyangiitis (MPA), Granulomatosis with Polyangiitis (GPA), previously called Wegener´s granulomatosis, and Eosinophilic Granulomatosis with Polyangiitis (EGPA), previously called Churg-Strauss granulomatosis [2]. AAV have an overall annual incidence of between 13 and 21 cases/million population. Their incidence varies according to geographical areas. In Spain, the annual incidence of GPA, MPA and GEPA is 4.9, 11.6 and 0.9 per million, respectively. Likewise, the incidence of AAV increases progressively with age, although they can appear at any age, and affect both sexes approximately equally. MPA is usually diagnosed in older patients than GPA and GEPA. Humoral immune mechanisms, related to the formation of ANCAs, and cellular immune and delayed-type hypersensitivity mechanism related to the formation of granulomas have been implicated in the pathogenesis of AAV. ANCAs, described in 1982, are specific autoantibodies directed against constituents of neutrophil granules and monocyte lysosomes [3]. They are classified according of indirect Immunofluorescence (IFA) patterns they produce in neutrophils and according to the target antigens against which they are directed. Typical IFA patterns of AAVs are cytoplasmic (C-ANCA) characterized by diffuse granular cytoplasmic fluorescence, directed against Proteinase 3 (PR3), and perinuclear (P-ANCA) with perinuclear fluorescence and nuclear extension, directed against Myeloperoxidase (MPO). GPA is primarily associated with ANCA-PR3, while MPA is primarily associated with ANCA-MPO. However, there is a percentage of MPA patients with ANCA-PR3 and of GPA patients with ANCA-MPO. The specificity of ANCAs seems to be of greater importance for the phenotype and prognosis of AAV than the classical GPA o PAM nomenclature [3]. ANCA-PR3 are associated with granulomatous inflammation, respiratory tract involvement, increased extra-renal involvement and higher relapse rate. ANCA-MPO are more associated with kidney-limited disease and worse renal prognosis [4]. Diagnosis of AAV is based on symptoms, laboratory findings of systemic inflammation, detection of ANCA, and characteristic histological findings. The relapse rate is higher in GPA than in MPA, with a cumulative rate of 50% of 5 years, and usually occurs within five years of diagnosis. Patients who are persistently ANCA positive after remission and those who become ANCA positive again are also at higher risk of relapse. However, treatment should not be changed in the absence of other data suggesting relapse [2]. The prognosis of AAV has improved dramatically following the introduction of glucocorticoid and cyclophosphamide and Rituximab therapy, with a 1-year survival of 93%, and 5 and 10-year survival of 79% and 75%, respectively. However, the overall risk of death in AAV patients is still 2.7 times higher than in the general population [2]. Age and creatinine at diagnosis are the factors associated with worse prognosis in terms of renal survival and mortality [2,5]. Mortality increases with age and doubles with each decade. Older patients and those who develop permanent organ damage at diagnosis have a higher risk of death. The main causes of mortality are renal failure, lung involvement and infections associated with immunos

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Citation: María Carmen Prados Soler, María Eugenia Palacios Gómez, María Dolores Salmerón Rodríguez, Isabel María Villegas Pérez and Francisco Javier González Martínez (2023) Relapse of P-ANCA Positive Vasculitis with Pulmonary Hemorrhage in Hemodialysis Patient. Therapeutic Challenge. J Nephrol Renal Ther 9: 075.

Received: January 01, 2023; **Accepted:** January 06, 2023; **Published:** January 17, 2023

uppressive therapy. The 5-year survival rate in MPA is lower than in GPA and ranges from 45% to 75%. The main causes of mortality are severe renal failure and infections. Survival in GEP is 60-97% at 5 years, and factors associated with worse prognosis are cardiomyopathy and gastrointestinal involvement.

Clinical Case

71-year-old woman at the time of admission in May/2022. Ten years earlier (February/2012), the patient had presented with hemoptysis and hematuria, together with deterioration of renal function (Cr 8 mgr/dl), arterial hypertension and constitutional syndrome. She was diagnosed with ANCA-MPO vasculitis with renal-pulmonary involvement. He received treatment with Plasmapheresis (PP), Corticosteroids (CS)+ Cyclophosphamide (CP) iv and maintenance with azathioprine which was modified to mycophenolate due to intense hyperuricemia. Follow-up in the Nephrology Department, with no new outbreaks but with progressive deterioration of renal function, so she started hemodialysis (HD) on 31/10/2017. She received cadaveric kidney transplant on 11/4/2018, with graft loss in January/2021, restarting HD 3 years later (21/1/2021). Every 6 months Ac-MPO is determined by protocol, always negative. In May/2022 the patient came to dialysis with more dyspnea and commented that she had reddish sputum (which she attributed to epistaxis). She reported weakness and asthenia in the previous weeks. Laboratory tests showed sudden anemia (Hb 7.9 g/dl) and a chest X-ray (Figure 1) showed an alveolar-interstitial infiltrate. AR without crackles. It was decided to transfuse 2 CH during dialysis, but there was a progressive increase in dyspnea and respiratory repercussions, requiring a 100% reservoir to maintain saturation. Due to high suspicion of a new outbreak, treatment was started with PP and CS. On physical examination, BP: 120/70 mmHg, with crackles in the right base on auscultation, no edema, no evidence of volume overload, no skin lesions or other notable alterations. Blood tests: Hb 7 g/dl, hematocrit 21%, leukocytes 10.970 (N 83%, L 7%), platelets 236.800, normal hemostasis, albumin 3.9 g/dl, normal liver profile, ferritin 120 ng/ml, PTH 155 pg/ml and negative serology for HCV, HBV, HIV. C-reactive protein 4.8. Pro-BNP > 35.000. Complement normal, anti-glomerular basement membrane negative. Subsequently, the diagnosis was confirmed with positive ANCA-MPO title 446 and a chest CT scan (Figure 2) showing diffusely distributed ground-glass lesions in the lung, findings due to alveolar hemorrhage.

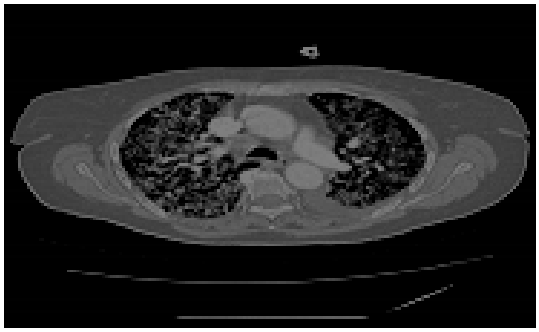

Figure 1: Chest CT scan on admission.

She completed treatment with PP (replacement with fresh plasma, total of 8 sessions)+MP iv pulses and then oral prednisone, in a descending pattern + CP iv (500 mgr on days 1 and 30) and Rituximab (RTX) (1 gram on days 2 and 16) with a very good clinical and

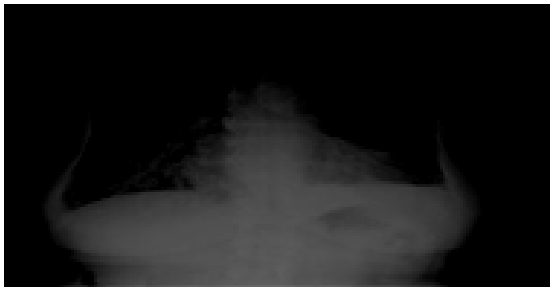

Figure 2: Chest X-ray on admission.

analytical response (including negative Ac-MPO). After 10 days the hemoptysis disappeared and radiological normalization was achieved after 3 weeks. In August/2022, admitted for bacterial pneumonia. Currently (7 months after relapse), the patient continues on periodic HD with no new incidences and receives biannual RTX doses of 1 gram until completing 2 years.

Discussion

ANCA-positive small-vessel vasculitis can cause the so-called reno-pulmonary syndrome. The most frequent cause of these processes is Good pasture's syndrome followed by Wegener´s granulomatosis, although there are series that report more than 50% of cases associated with ANCA-positive pauci-immune glomerulonephritis [6-8]. Our patient has a reno-pulmonary syndrome, with positive p-ANCA and pauci-immune glomerulonephritis at the beginning of her diagnosis, with subsequent recurrence under HD treatment. Advanced age, the presence of arterial hypertension or the existence of proteinuria or impaired renal function (serum creatinine > 4.5 mg/dl) at the onset of diagnosis are risk factors for the development of Chronic Renal Failure (CRF) and the need for renal replacement therapy. Kaplan-Pavlovcic's work on 37 elderly patients with rapidly progressive glomerulonephritis and positive ANCA confirmed these risk factors. Subsequently, the European Vasculitis Study Group (EUVAS) found that decreased glomerular filtration rate and chronic anatomopathological lesions at diagnosis are strong predictors of the development of end-stage renal disease. Approximately 20% of pauci-immune vasculitis develop stage 5 CRF. In turn, the existence of respiratory tract involvement implies a worse prognosis. Relapses are not common and occur is smaller numbers in kidney transplant and HD patients [9]. Recurrence in HD can vary between 10-30% per patient/year according to the various studies that exist and is higher than in patients with kidney transplant. The mechanisms of altered immune response, especially cell-mediated, in this type of patient are multiple but remain unclear at present. The usefulness of ANCAs in monitoring disease activity is controversial in patients on HD. In our case, relapse coincided with significant ANCA title positivity, which became negative after treatment [4].The treatment of relapses in either kidney transplant or HD does not differ from the usual treatment [9]. Patients with minor relapses can be controlled by increasing the doses of oral therapy they were receiving. Patients with relapses usually require reintroductions of initiation of one or more immunosuppressive agents (CS, CP, RTX, immunoglobulins intravenous) to achieve disease control. The role of plasma exchange as a component of induction therapy has been defined as useful in 2 specific populations:

1. Life-threatening pulmonary hemorrhage and 2) patients with dialysis-dependent renal failure at presentation.

2. RTX therapy has been shown to be higher to conventional treatment in the control of patients with GPA or PAM and multiple relapses, so its use is recommended over that of CP or other immunosuppressants.

In some patients with relapsing, aggressive forms, sequential therapy with RTX and CP may be useful. In fact, the FDA has already approved the combination of RTX + CS as first-line therapy for remission induction in VAA [2,9]. In patients treated with RTX, it is recommended that serum gamma globulin levels be determined before each treatment cycle. Vaccination for pneumococcal and influenza viruses is recommended for all AAV patients [9]. It has been suggested that B-lymphocyte killing with anti-CD20 antibodies (RTX) may has a favorable effect on AAV by eliminating the cells responsible for producing ANCAs. There are at least 10 case series reporting its use with promising results in maintaining patients in complete remission and negative ANCA titles. A complete remission rate has been described in 2-6 months around 75% using RTX, with peripheral B-lymphocyte depletion through CD19 determination and ANCA negativization; however, lymphocyte recovery is expected at 10 months, which constitutes a risk of relapse, so its use in repeated doses has been described as a preventive measure. However, the medium and long-term risks of using these drugs must be considered, which requires close monitoring of patients. Patients on HD may suffer relapses of vasculitis but are also at high risk of infections and cardiovascular events, which calls into question the maintenance of therapy (4 months vs 2 years). The addition of anti-complement therapy (Avacopan) has been proposed to reduce some of the toxicity due to standard therapy including the risk of infections. The latest therapies to be tested for AAV are complement inhibitors, due to the recent understanding of the role of alternative complement pathway activation in neutrophil activation and migration. The recently published ADVOCATE trial is a phase 3 randomized controlled trial comparing Avacopan (a C5a receptor inhibitor) with standar CS therapy in addition to CP/azathioprine or RTX induction therapy. The study demonstrated non-inferiority for the clinical endpoint and may provide an option for a steroid-sparing regimen for patients in the future. Additional anti-C5a therapies are currently being studied in phase 2 trials. Finally, an upcoming randomized clinical trial from France will investigate whether complete withdrawal of immunosuppression in patients with AAV on dialysis is not inferior to the standard of care, and will provide more information on how quickly immunosuppression can be reduced. At present, avacopan is not licensed for use in patients with a glomerular filtration rate of less than 15 ml/min, so we did not prescribe this drug in our patient [8].

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