Relapsing p-ANCA positive vasculitis with lung hemorrhage in a patient on hemodialysis

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SUMMARY

Relapses of p-ANCA vasculitis during chronic dialysis treatment are infrequent. We report a patient with a pulmonary-renal syndrome and p-ANCA vasculitis who relapsed one year after starting hemodialysis treatment. Treatment with steroids and cyclosphosphamide successfully controlled the relapse, though cyclophosphamide had to be discontinued because of leucopenia. Clinical features of renal vasculitis, relapse after dialysis, the usefulness of ANCA titles as possible predictors and therapeutic options are discussed.

Key words: *Vasculitis. Pauciinmune. Pulmonary hemorrahge. p-ANCA. Crescentic. Dialysis..*

RESUMEN

Las recaídas en el curso de las vasculitis p-ANCA en los pacientes en diálisis son poco frecuentes. Revisamos el caso de una paciente diagnosticada de vasculitis p-ANCA que desarrolló una recaída con síndrome reno-pulmonar un año después de iniciar tratamiento sustitutivo con hemodiálisis. El tratamiento con esteroides y ciclofosfamida controló el cuadro, pero ésta última hubo de suspenderse por leucopenia. Se discuten los cuadros de vasculitis con afectación renal y ulterior recaída en diálisis, la utilidad de los títulos de ANCA para predecir esas recaídas y las opciones terapéuticas.

Palabras clave: Vasculitis. Pauciinmune. Hemorragia pulmonar. p-ANCA. Semiluna. Diálisis.

INTRODUCTION

ANCA are serological markers directed against several components of neutrophil cytoplasm, and are considered activity factors in necrosing pauci-immune vasculitis such as Wegener granulomatosis, microscopic polyangiitis, or Churg-Strauss syndrome.[1,2] p-ANCA-positive vasculitis may cause isolated renal damage or involve other target organs, particularly the lung, in which latter case it is called pulmonary-renal syndrome.[3] Relapse is not very common and even less in patients on dialysis.[4] The need for renal replacement treatment is not frequent either.[5] Immunosuppressive treatment and dialysis itself increase the risk of infectious complications.[6] Relapse of a p-ANCA vasculitis with pulmonary-renal involvement during chronic hemodialysis treatment is reported.

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CASE REPORT

A 73-year-old female patient. She had been admitted to hospital four years before for hemoptysis and hematuria with kidney function impairment (Cr 7 mg/dL), high blood pressure, and constitutional syndrome. She had proteinuria with microhematuria and blood casts, and positive p-ANCA (39 U) were found in her immunological study, that was otherwise negative (c-ANCA, anti-GBM, cryoglobulins, HBV, HCV and HIV serology, lupus anticoagulant, and antiphospholipid antibodies). A renal biopsy showed fibrous occlusive crescents in glomeruli, with ischemic lesions in the vascular tangle, intact arterial vessels, and severe interstitial fibrosis with lymphoplasmocyte infiltration. Immunofluorescence was negative. Patient was diagnosed of p-ANCA-positive vasculitis with pulmonary-renal involvement and type III extracapillary proliferative glomerulonephritis (pauci-immune). Treatment was then started with intravenous boluses of 6-methylprednisolone, followed by prednisone (1 mg/kg/day) and oral cyclophosphamide at a dose of 1.5 mg/kg/day. Cyclophosphamide was discontinued at one month of treatment due to leukopenia, and azathioprine was started and continued for 2 years. Steroid treatment was tapered to discontinuation during the first year. Though clinical response was favorable, kidney function did not normalize and renal replacement treatment was required 3 years after diagnosis. No complications occurred during this time, except for a trend to leukopenia, and p-ANCA remained negative. One year after the start of hemodialysis, the patient experienced isolated hemoptysis with no fever or other related clinical signs. Physical examination revealed a BP of 120/70 mmHg, crackling sounds in the right base on auscultation, no edema or data suggesting volume overload, and no skin lesions or other remarkable changes. Laboratory tests results included: Hb: 11.8 g/dL, hematocrit: 36%, WBC: 7400 (N: 83%, L: 7%); platelets: 376,000, normal hemostasis, albumin; 3.9 g/dL, normal liver profile, ferritin: 120 ng/mL, PTH: 155 pg/mL, and negative serological tests for HCV, HBV, and HIV. Immunological study was posi-

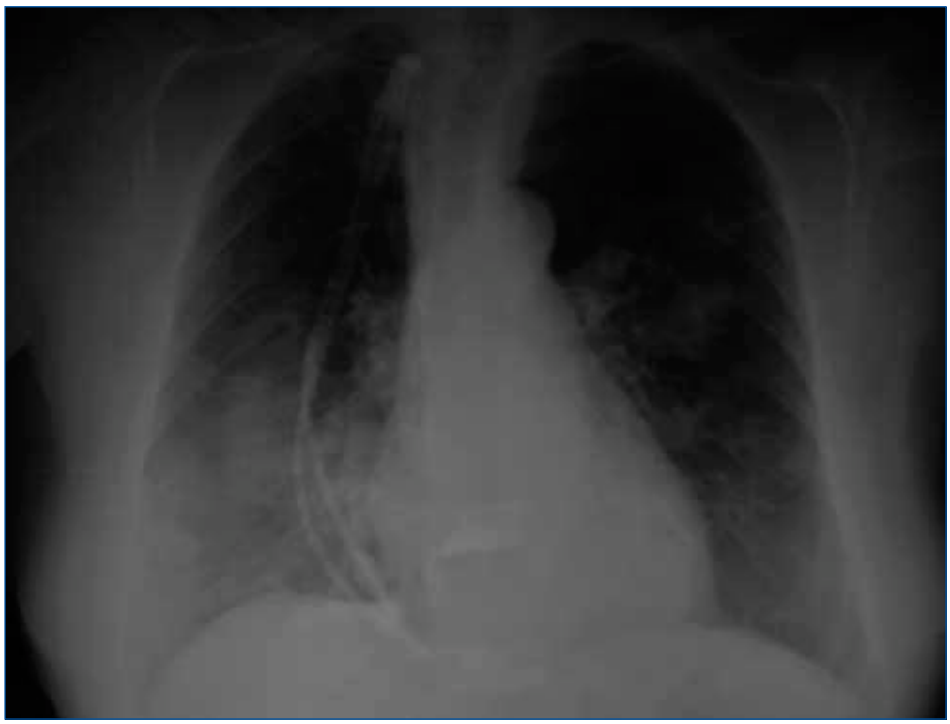

Figure 1. Chest X-rays. Diffuse, bilateral cottony infiltrates on admission.

tive for p-ANCA (33.3 U) and negative for all other parameters, with normal complement. Chest X-rays revealed the presence of diffuse, bilateral cottony infiltrates (fig. 1) and a CT scan of the chest showed diffuse peripheral bilateral lung involvement, mainly at the bases, with heterogeneous opacities. No cavitations or calcifications were seen (fig. 2). Based on the findings and on the evidence of disease relapse, treatment was started with steroid bolus (3 days, 250 mg IV), followed by oral prednisone at a dose of 1 mg/kg/day with subsequent tapering, and oral cyclophosphamide (1.5 mg/kg/day). After one month of treatment, the patient experienced a new episode of leukopenia that required cyclophosphamide discontinuation. Clinical course was however favorable, with disappearance of hemoptysis at 40 days of treatment and radiographic normalization at 3 weeks. One year later, she is on a tapering steroid treatment and has experienced no new episodes of hemoptysis. Titer of p-ANCA became negative at 2 months.

DISCUSSION

Small vessel vasculitis with positive ANCA may cause the so-called pulmonary-renal syndrome.[7,8] The most common cause of this condition is a Goodpasture syndrome, followed by Wegener's granulomatosis,[5,9] though some series have reported more than 50% of cases to be associated to ANCA-positive pauci-immune glomerulonephritis.[7] Our patient had a pulmonary-renal syndrome with positive p-ANCA and pauci-immune glomerulonephritis on initial diagnosis, and experienced a subsequent relapse while on hemodialysis (HD).

Advanced age, high blood pressure, or existence of proteinuria or impaired kidney function (serum creatinine > 4.5 mg/dL) on initial diagnosis are risk factors for the development of chronic renal failure (CRF) and the need for replacement therapy. The Kaplan-Pavlovcic study on 37 elderly patients with rapidly progressive glomerulonephritis and positive ANCA supported these risk factors.[10] The European Group for the Study of Vasculitis (EUVAS) subsequently documented that a decreased glomerular filtration rate and chronic pathological lesions at the time of diagnosis are powerful predictors for the development of end-stage renal disease.[11] Chronic end-stage renal failure occurs in approximately 20% of patients with pauci-immune vasculitis.[6]

The existence of respiratory tract involvement is in turn associated to a poorer prognosis.[12] In a retrospective study of 14 patients with pulmonary-renal syndrome, Gallagher and colleagues showed a 36% mortality rate, with 85% and 67% survival rates after the first and second years respectively.[3] In another study of 22 patients with pulmonary-renal syndrome and small vessel vasculitis, the mortality rate at the end of the study reached 50%.[13] In a large retrospective study conducted by Weidner et al on 80 patients with similar characteristics, a 26% mortality rate was reported. One- and 5-year survival rates were 86% and 81% respectively. These authors found an overall relapse rate of 33%, similar to other studies.[14]

Disease recurrence after HD is started or a kidney transplant (KT) is received is not clear. Mechanisms altering immune response, particularly cell-mediated immune response, in these patients are multiple, but continue to be ill-defined.[15] In the Gera et al study on 35 patients with vasculitis and positive ANCA undergoing KT, only 3 relapses with no renal involvement were seen, and no clear risk factor could be evidenced.[16] In a prior study by Roasting on 8 patients with similar characteristics and KT, only one relapse with pulmonary-renal involvement was seen.[17] Other studies found simi-

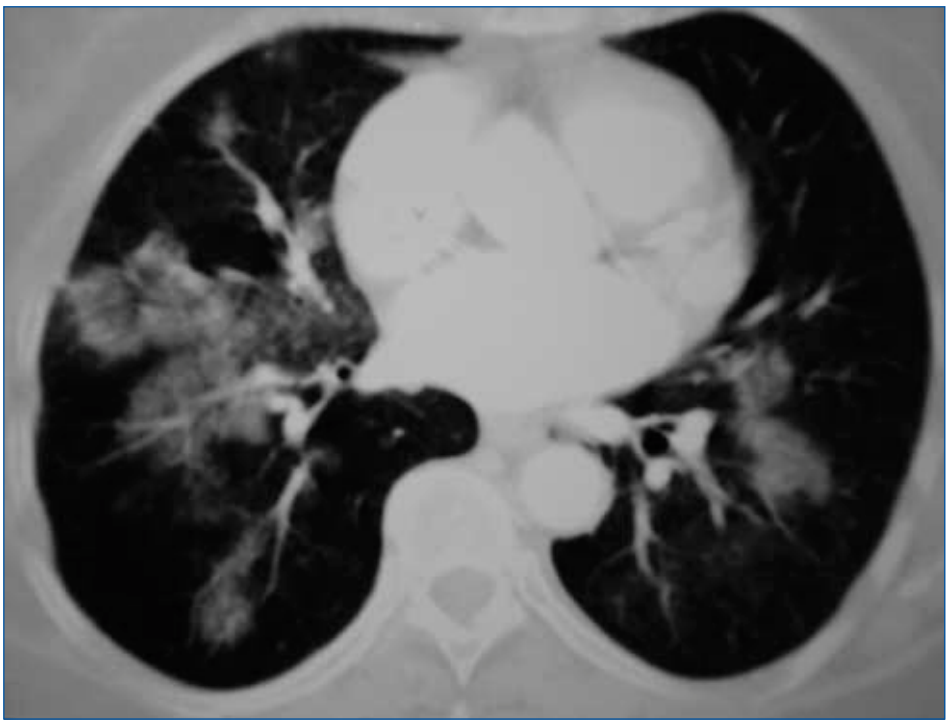

Figure 2. CT scan. Heterogeneous opacities with air bronchogram in alveolar location.

lar favorable results, but reported that immunosuppressive treatment does not fully protect from relapse.[18,19]

Recurrence while on HD has rarely been reported. In the retrospective study of case series conducted by Weidanz et al, among the 46 patients in whom recurrence was analyzed, a lower relapse rate was seen in patients on HD as compared to pre-dialysis patients with a similar condition (0.05 *vs* 0.13 relapses/patient/year), though the number of infections was higher in the HD group.[4] Recurrence on HD may range from 10%-30% per patient/year depending on the study, and is more common than in KT patients.[6,20]

Treatment of relapses occurring in either KT or HD patients does not differ from standard treatment. Allen, in a retrospective review of 59 patients with vasculitis and associated ANCA who were on HD or had received a KT, noted that relapse usually responded to cyclophosphamide and steroids.[20] Booth et al, in a multicenter, retrospective study on a cohort of 246 patients, showed that relapse occurred in 34% of their patients and reported that, though medical treatment had improved prognosis, morbidity and mortality continued to be high, particularly in association to leukopenia, that was found in up to 41% of cases.[21] The European group (EUVAS) designed a randomized study including 155 patients with vasculitis and positive ANCA with the objectives of minimizing complications and optimizing treatment. This group concluded that replacement of cyclophosphamide by azathioprine in the remission phase did not increase the risk of relapse.[22] Other therapeutic options have not been adequately documented yet. Conventional treatment was started with steroids and cyclophosphamide for the relapse occurring in our patient. The trend to leukopenia required discontinuation of cyclophosphamide and advised against use of azathioprine. The relapse was associated to a new increase in autoantibody titers, but the test became negative after immunosuppressive treatment.

The value of antibodies for monitoring disease activity in patients on HD is controversial. In the Weidemann et al cross-sectional study of 1277 patients on HD, positive p-ANCA and c-ANCA titers with no evidence of vasculitis were found in 5% of cases.[23] Positive ANCA with no disease were also seen in another study of 335 patients, 176 of whom were on HD, and positive titers were related to an increased cytokine formation in patients on dialysis.[24] Other studies, such as those by Gordon and Gaskin, reported conflicting results regarding the presence of antibodies in disease relapses.[25,26]

To sum up, vasculitis is uncommon, but is associated to significant complications and to a poor outcome in many cases. However, relapse is not common, and even less so in kidney transplant and hemodialysis patients. Patients on HD are treated similarly to those without HD, but have a greater risk of infectious complications because of leukopenia. The value of ANCA titers as activity markers in hemodialysis has not been defined yet.

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