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Case Report

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Relapsing MPO Positive Vasculitis with Lung Hemorrhage in a Patient on Hemodialysis

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Abstract

The Antineutrophil Cytoplasmic Antibody (ANCA) associated vasculitisisa rare multisystem auto-immune disease. Long-term immunosuppressive therapy with corticosteroids and cyclophosphamide or rituximab is currently considered the gold standard treatment to achieve remission, however without avoiding relapses. Approximately, 20% of patients with ANCA vasculitis develop End Stage Renal Disease (ESRD). It has been reported that the recurrences of ANCA vasculitis on chronic dialysis are infrequent. We, herein, describe a 74-year-old patient who was, initially, diagnosed with renal limited P-ANCA vasculitis and ESRD and presented with lung involvement and pulmonary hemorrhage two years after starting hemodialysis treatment.

Background

The Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis (AAV) is a collection of relatively rare autoimmune diseases of unknown cause, characterized by inflammatory cell infiltration causing necrosis of blood vessels. The AAV comprise granulomatosis with polyangiitis (GPA, previously known as Wegener's granulomatosis), Microscopic Polyangiitis(MPA) and eosinophilic granulomatosis with polyangiitis (EGPA, previously known as Churg-Strauss syndrome).The clinical spectrum of P-ANCA vasculitis is wide and may be renal limited or multisystem disease. The use of immunosuppressive treatment including cyclophosphamide and glucocorticoids improved the prognosis of untreated AAV to one of where long-term remission was possible but relapses are common. The need for chronic renal replacement treatment is not frequent but it seems that chronic dialysis may result in a relative quiescence of the autoimmune process so relapses of p-ANCA vasculitis during chronic dialysis treatment are infrequent either.

We report a patient with renal limited P-ANCA vasculitis syndrome who relapsed two years after starting hemodialysis treatment.

Case Presentation

A 74 years old male patient presented in emergency department with worsening normochromic and normocytic anemia, which required blood transfusions the last 8 months. His past medical history was significant for End Stage Renal Disease due to P-ANCA positive glomerulonephritis, which was diagnosed 4 years ago. He has been admitted to hospital four years ago with kidney function impairment (Cr: 7,8 mg/dl), hematuria and blood castsand positive P ANCA were found in his immunological study. A renal biopsy showed focal necrotizing and cresentic glomerulonephritis. Immunofluorescence was negative. The patient was diagnosed of p-ANCA-positive glomerulonephritis (pauci-immune) without extrarenal manifestations. Consequently, treatment with intravenous boluses of methylprednisolone was submitted, followed by prednisone (1 mg/kg/day) and iv cyclophosphamide at a dose of 10 mg/kg/15 days. Steroid treatment was tapered to discontinuation during the first 2 years. Though clinical response was favorable, kidney function did not normalize and renal replacement treatment was required 2 years after diagnosis, with discontinuation of immunosuppressive therapy.

No complications occurred the following two years while he was in chronic hemodialysis treatment, though the patient remained without observation as it concerns the primary disease.He was admitted to renal department with worsening normochromic and normocytic anemia, which required blood transfusions, iron replacement therapy and the highest dose of erythropoietin for a hemodialysis patient, for the last 8 months. He did not however

experience hemoptysis, fever, cough, GI bleeding or other related clinical signs. Physical examination revealed a BP of 120/70 mmHg, normal breathing sounds on auscultation, no edema or data suggesting volume overload, and no skin lesions or other remarkable changes. Laboratory tests results included: Hb:9,1 g/dL, hematocrit:29,5%, WBC:6,330/ul(N: 80%, L: 12,6%); platelets:137.000, normal homeostasis, albumin:3,8 g/dL, normal liver profile, ferritin:591 ng/mL, PTH: 100 pg/mL, CRP:32mg/l , ESR:35 mm and negative serological tests for HCV and HBV. A positive QuantiFERON- TB GOLD was detected. Immunological study was positive for p-ANCA and MPO (45units) and negative for all other parameters including anti-GBM, with normal complement. Chest X-rays were normal but a CT scan of the chest showed diffused bilateral lung involvement, ground glass lesions, non-cavitating nodule 8mm at the right upper lobe. No cavitations or calcifications were seen.

In view of the above findings, the patient underwent a bronchoscopy which did not reveal active hemorrhage but only a hemorrhagic mucosal and negative cultures for mycobacterium tuberculosis and other common pathogens. Also, a bone marrow biopsy occurred, without abnormal findings and gastrointestinal endoscopies with findings that did not explain the undergoing anemia. Based on the evidence of relapsing P-ANCA positive vasculitis with pulmonary involvement, treatment w with steroid bolus (3 days, 500 mg IV) started, followed by oral prednisone at a dose of 1 mg/kg/day and the first cycle of iv cyclophosphamide (10 mg/kg/14 days), based on Cyclops protocol. Furthermore, he received isoniazid prophylactic therapy for the prevention of tuberculosis. The patient was discharged with stabilization of hematocrit and good clinical status.

He returned 15 days later for the second cycle of IV cyclophosphamide and during his admission he presented worsening cough and hemoptysis. Physical examination revealed a BP of 130/80 mmHg, crackling sounds in all lung fields, especially in the right lung on auscultation, no edema or data suggesting volume overload. Laboratory test results included: Hb:8,4 g/dL, hematocrit:26,4%, WBC: 9.610/ul(N: 94%, L: 1,2%); platelets:134000, normal homeostasis, albumin:3,5g/dL, normal liver profile, CRP:107 mg/l , ESR:17 mm. Chest X-rays revealed the presence of diffuse cottony infiltrates at the left lung and a CT scan of the chest showed diffuse peripheral bilateral lung involvement, mainly at the left lung. Based on the evidence of diffuse pulmonary hemorrhage, we concluded in admission of plasmapheresis (60ml plasma volume/kg) in the initial induction therapy and we performed a combination of rituximab-cyclophosphamide therapy. The patient underwent 10 plasmapheresis cycles, iv cyclophosphamide (10mg/kg-Cyclops protocol) and iv Rituximab (1000 mg) in two divided doses separated by two weeks. Clinical course was favorable, with disappearance of hemoptysis at 10 days of treatment and improvement of the radiographic findings at 5 days. The patient was discharged with good clinical status.

Discussion

Patients with ANCA vasculitis may present with renal-limited disease or/and with a variety of extrarenal clinical manifestations affecting one or several organ systems. In the five-year retrospective study of Booth et al 33% of the patients had renal-limited disease[1].Pulmonary involvement is a characteristic feature of AAV. Diffuse Alveolar Hemorrhage (DAH) occurs as a consequence of pulmonary capillaritis in the ANCA-associated vasculitis and affects about 10% of patients with ANCA GN, and is associated with an increased risk of death. In a proportion of 20-30% rapidly progressive GN that occurs in patients with ANCA vasculitis resulting in End Stage Renal failure and dialysis treatment[2]. Our patient had a renal limited vasculitis with positive p-ANCA and pauci-immune glomerulonephritis on initial diagnosis which lead to chronic dialysis treatment and experienced a subsequent relapse while on Hemodialysis (HD) and pulmonary hemorrhage while on immunosuppressive therapy.

Disease recurrence after HD started is not clear. Chronic dialysis may result in a relative quiescence of the autoimmune process[3]. In retrospective analyses of patients with ANCA vasculitis, the relapse rates of vasculitis were about 60% lower in patients with ESRD (KDIGO).There is a paucity of literature to guide therapy of patients requiring dialysis, particularly relating to immunosuppression and it consists a matter of controversy. The lower rate of relapse contrasts with the high rate of infection and the toxicity associated with immunosuppression on dialysis patients [2]. In the series of Haubitz et al, they reported a death caused by leucopenia in 1 patient and early discontinuation of therapy because of severe adverse effects in 3 patients[4]. A few series have been conducted regarding the risk-benefit ratio of continued maintenance therapy. In the series of Weidanz et al and Lionaki et AL, consideration has been given to early discontinuation of cytotoxic immunosuppressive treatment in patients requiring dialysis therapy[2,3]. However, only limited conclusions can be drawn of these reports.

Based on cohort studies, risk factors for relapse include persistence of PR3-ANCA (compared to MPO-ANCA), history of upper respiratory tract disease, or lower respiratory tract disease. Patients with any of these three risk factors have an approximately 1.7-fold increased risk of relapse, and those with all three risk factors have an approximately 4.7-fold increased risk of relapse (KDIGO). It has been known that the relapse rate of ANCA vasculitis among patients on chronic dialysis is substantially lower compared with that among patients with preserved renal function[5]. In the retrospective study of Allen et all thirty-seven of the fifty-nine patients received dialysis and 7 of them had a recurrence of the primary disease[5].Treatment of relapses of ANCA vasculitis

is the same as the induction therapy and does not differ in patients on HD. 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[5]. However, there are cases which require the addition of plasmapheresis to initial therapy (pulmonary hemorrhage) and some known as resistant disease in which is recommended the addition of Rituximab. Resistant disease is defined as the persistence of or appearance of kidney and/or systemic manifestation of vasculitis, while receiving treatment equal in intensity to initial immunosuppressive therapy (KDIGO).

In addition, it has been reported the use of Rituximab combined with cyclophosphamide and corticosteroids in an attempt to more rapidly attain remission and minimize exposure and side effects of corticosteroids and cyclophosphamide, specifically in patients with relapse who had already received high cumulative dose of cyclophosphamide. In the retrospective study of Cortazar et al 129 patients with newly diagnosed or relapsing ANCA vasculitis 84% of patients were in complete remission at 5 months, and all surviving patients ultimately achieved complete remission[6]. Moreover, in the RITUXVAS trial and in the regimen reported by Mansfield et al[7]. combined rituximab and i.v cyclophosphamide with favorable outcomes.Conventional treatment started with steroids and cyclophosphamide for the relapse occurring in our patient, however with the appearance of pulmonary hemorrhage while on immunosuppressive therapy (by oral prednisone at a dose of 1 mg/kg/day and the first cycle of iv cyclophosphamide) we decided the addition of plasmapheresis and Rituximab.

Based on current guidelines no maintenance therapy is recommended to patients who are dialysis-dependent and have no extrarenal manifestations of disease. Though as in our patient's case nephrologists should consider the possibility of extra renal manifestation even if the disease appears initially as renal limited, strong suspicion particularly when anemia of not known origin occurs.

Conclusion

ANCA vasculitis is a rare condition with high morbidity and mortality rate. Recurrences of the disease are not common, and even less so in kidney transplant and hemodialysis patients. Treatment of relapse is the same as the initial therapy and does not differ when the relapse occurs in patients on HD. The addition of Rituximab in the initial therapy may has favorable results.

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