

CLINICAL VIGNETTE

ANCA Vasculitis: Beyond Steroids and Cyclophosphamide In Patients with Renal Impairment

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Introduction

Kussmaul and Maier first described the clinical entity of anti-neutrophil cytoplasmic autoantibody mediated vasculitis (ANCA) in 1866¹. However, it was not until 1988 when the causative antibodies were discovered². Prior to the advent of effective medical therapy ANCA vasculitis was considered incurable with a mortality rate of 93% within 2 years of diagnosis³. Over the past 30 years, progress has been made with survival now approaching 80% at 5 years post diagnosis. More recently in the past decade efforts have been made to reduce the toxicity of the standard glucocorticoid and cyclophosphamide regiment.

Case Presentation

A 67-year-old female with a history of idiopathic pulmonary fibrosis, urinary retention, and GERD was found to have new onset anemia, hemoglobin 7.3 g/dL, and an elevated creatinine, 6.3 mg/dL, on routine laboratory studies performed by her primary care physician. Two months prior her labs had been normal.

The patient reported being in her normal state of health until approximately three days prior to admission. She underwent EGD for a persistent abdominal pain and early satiety for 3 months that revealed a hiatal hernia, but was otherwise unremarkable. Following the procedure the patient developed a sore throat with hemoptysis, which had been steadily improving. She also noted worsening of her urinary retention, but denied any changes in the amount of urine or its color. Her only medication at the time was omeprazole 20 mg daily. She denied any over the counter or herbal medication use.

On physical examination, the patient had a temperature of 36.9 °C, a pulse of 110 beats per minute, blood pressure of 134/81 mmHg, respiratory rate of 24 with a pulse oximetry reading of 97% on room air. Her exam was notable for diffuse bilateral inspiratory crackles. Her head was normocephalic and atraumatic. ENT exam was unremarkable with

no nasal crusting. Heart was regular rate with no murmurs. Her abdominal exam was benign with no masses palpated. Her extremities were warm and dry to touch with no edema, and there were no skin rashes.

Laboratory data showed a white blood cell count of 14.05×10^3 , hemoglobin of 7.3 g/dL, hematocrit of 22.7 and platelet count of 518. Her serum chemistries were notable for a serum sodium of 128 mEq/L, potassium of 5.4 mEq/L, bicarbonate of 19 mEq/L, BUN 65 mg/dL, and creatinine 6.3 mg/dL. Chest CT confirmed her prior diagnosis of IPF without interval changes from prior imaging.

The patient was initially treated with intravenous saline and underwent work up for her acute kidney injury, including renal ultrasound and urinalysis. Her renal ultrasound showed no evidence of hydronephrosis and normal kidney size and echogenicity. The urinalysis was remarkable for 10 red blood cells, 30 white blood cells and 31 squamous epithelial cells. Given the acuity of her renal impairment she underwent percutaneous native kidney biopsy, which revealed pauci-immune crescentic glomerulonephritis with severe injury in 5 of 8 glomeruli and small vessel vasculitis. Serological work up confirmed the presence of P-ANCA titer of 1:320.

Discussion

Since 1979, the standard of care for ANCA vasculitis with relatively preserved renal architecture has been a combination of high dose glucocorticoids and oral cyclophosphamide (2 mg/kg) for induction with ongoing low dose steroids and oral cyclophosphamide for maintenance therapy⁴. Patients with severe interstitial fibrosis on biopsy are unlikely to have renal recovery and immunosuppression may be unwarranted. While this regimen has been effective in improving clinical outcomes in patients with ANCA vasculitis there is still an unmet clinical need for better therapies. In particular is the concern for cumulative cyclophosphamide dose related

toxicities of myelosuppression, infection, urothelial malignancy, and infertility. Furthermore, it is estimated that 50% of patients experience a relapse after discontinuation of cyclophosphamide, especially those with concurrent lung disease.

In the past 20 years several investigators have looked at reducing cyclophosphamide exposure, either by reducing the dose or avoiding the medication all together. The first study to explore replacement of cyclophosphamide was the CYCAZERM trial⁵. In this study, 155 patients with an average serum creatinine of 5.7 mg/dl were induced with prednisone and cyclophosphamide for 3 months prior to undergoing maintenance randomization to either continue oral cyclophosphamide at 1.5 mg/kg or azathioprine 2 mg/kg in combination with prednisone for a total of 18 months following the index event. There were 8 deaths, 7 in the first 3 months prior to randomization, and no differences in the relapse rate between groups. demonstrating that the cyclophosphamide exposure can be safely avoided during the maintenance phase of treatment.

The CYCLOPS trial, looked at further reducing cyclophosphamide exposure by administering intravenous pulse cyclophosphamide rather than oral cyclophosphamide during the induction phase of treatment⁶. In this study 149 patients were randomized to either pulse cyclophosphamide 15 mg/kg every 2-3 weeks for 3 months or oral cyclophosphamide 2 mg/kg daily for 3 months followed by azathioprine 2 mg/kg as maintenance therapy until month 18. Remission rates were similar in both groups after 9 months and the intravenous group had significantly less cumulative cyclophosphamide exposure compared to the oral group, 8.2 gm versus 15.5 gm, respectively. Long-term studies have demonstrated an increased risk of recurrence using intravenous cyclophosphamide, but no change in mortality.

In an effort to further reduce cyclophosphamide exposure two studies have looked at rituximab, a CD20 monoclonal antibody, for induction therapy. The RAVE trial randomized 197 patients with ANCA vasculitis to either rituximab 375 mg/m² weekly for four weeks versus oral cyclophosphamide 2mg/kg for 3 months⁷. Both groups received steroid therapy and the cyclophosphamide group received azathioprine maintenance, whereas the rituximab therapy group did not receive any additional immunosuppressive therapy. At six months there was equal efficacy in terms of remission and in the 18 month follow up study remission was also similar between both

groups⁸. The notable exclusion criteria were a creatinine > 4.0 mg/dL and pulmonary disease.

The RITUXIVAS trial looked using rituximab in patients with ANCA-associated vasculitis and renal impairment, with estimated GFR at time of enrollment being 18 ml/min. In this trial 44 patients were randomized in the 3:1 ratio to either rituximab 375 mg/m² weekly for four weeks with two intravenous doses of cyclophosphamide versus intravenous cyclophosphamide 2mg/kg for 3 months followed by azathioprine maintenance. One-year outcomes revealed non-inferiority of the rituximab therapy arm, with a trend towards superiority in patients with recurrent disease.

Combined these studies suggest that cyclophosphamide dosages can be reasonably reduced to avoid long term exposure either through a dose reduction on induction or by avoidance by substituting rituximab during induction and azathioprine during maintenance if cyclophosphamide is used for induction therapy.

In addition to immunosuppressive therapy plasmapheresis has been demonstrated to have beneficial renal outcomes in patients with severe ANCA-associated vasculitis and renal impairment. In the pivotal MEPEX trial 137 patients with ANCA-associated vasculitis and significant renal impairment defined as either requiring dialysis or a serum creatinine > 5.8 mg/dL were randomized to receive plasmapheresis in addition to immunosuppressive therapy⁹. Compared to immunosuppression alone, the addition of plasmapheresis reduced the risk of dialysis dependence from 43 to 19%, although patient survival was unchanged.

Conclusion

This patient with severe renal impairment from ANCA-associated crescentic glomerulonephritis was treated with high dose glucocorticoids and intravenous rituximab 375 mg/m² weekly for four weeks. We had offered her the choice of cyclophosphamide but she refused due to concerns about cancer risks. She was initiated on hemodialysis for renal impairment and started on plasmapheresis in the hospital. She was discharged on maintenance dialysis. Nine months after induction she remains on low dose prednisone 10 mg and is has been off dialysis with a creatinine of 2.6 mg/dL for three months. She has not had any signs of relapse to date.

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