CLINICAL VIGNETTE

ANCA Antibodies with Moderate Proteinuria Associated with Transitional Cell Carcinoma, an ANCA Flare due to Malignancy

The ANCA-malignancy link

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Introduction

Anti-neutrophil cytoplasmic antibodies (ANCA) are the etiologic antibodies that causing ANCA-associated vasculitis (AAV). These antibodies generally occur in the perinuclear pattern (in microscopic polyangiitis –MPA, or Eosinophilic granulomatosis with polyangiitis E-GPA), or as cytoplasmic pattern (in Granulomatosis with polyangiitis GPA). These antibodies are not always pathogenic, and can occur as a false positive cross-reactive serological marker in patients with hepatitis C. Rarely, some hepatitis C infected patients can have AAV.2

Nonvasculitic ANCA antibodies are also seen in malignancy.3 Malignancy is often associated with true ANCA vasculitis, even with treatment with cytotoxic alkylating agents like cyclophosphamide.4 Prevalence of Lymphoma, leukemia bladder carcinoma, and non-melanoma skin cancers was elevated in patients with treated ANCA disease.4,5 ANCA presence does not guarantee pathogenicity and the presence of these markers without vasculitis may be due to a possible underlying malignancy.6 We report a 78-year-old female with previous ANCA vasculitis (GPA subtype) treated previously with Ponticelli protocol (oral steroids and cyclophosphamide) who developed proteinuria and rising ANCA titers along with hematuria. Renal function remained stable, and there were no pulmonary symptoms. An ultrasound of the bladder revealed a bladder tumor, and immediately after removal of the bladder the proteinuria decreased to low levels with preserved renal function. Subsequently, however, her serological markers and proteinuria rose again indicating likely recurrence of AAV.

Case Report

A 78-year-old Caucasian female had been treated for GPA almost 30 years ago with Ponticelli protocol (oral steroids and cyclophosphamide) who developed proteinuria and rising ANCA titers along with hematuria. Renal function remained stable, and there were no pulmonary symptoms. An ultrasound of the bladder revealed a bladder mass, and immediately after removal of the bladder the proteinuria decreased to low levels with preserved renal function. Subsequently, however, her serological markers and proteinuria rose again indicating likely recurrence of AAV. She presented with concern for another flare, although she had no respiratory symptoms. Developed foam in her urine as well as hematuria and her urinary protein to creatinine ratio showed between 0.6 to 1 gram of protein/gram creatinine. Her serum creatinine was within normal limits. An ANCA titer was increased from <1:20 to 1:40 to 1:80. Renal ultrasound and additional labs did not indicate any cause of proteinuric glomerulonephritis.

Renal and bladder ultrasound revealed a 3.4cm bladder tumor suspicious for urothelial carcinoma. It was decided to resect the mass because of the association between ANCA disease and malignancy. Her hematuria and proteinuria could have been from either the mass itself, bleeding, or to a malignancy associated secondary membranous GN. After resection and local treatment of the bladder cancer, the proteinuria improved with maintained renal function, but the ANCA antibody titers did not decrease. However, there was no clinical evidence for active vasculitis.

Within a month after mass removal c-ANCA titers increased to their highest historical level at 1:80 titer. Serum creatinine rose from 1 to 1.2, and urinary protein to creatinine ratio increased from 0.3 gram protein/gram creatinine to 0.9-1 gram protein/gram creatinine (see Figure 1). A renal biopsy revealed a crescentic glomerulonephritis as expected for an active ANCA associated vasculitis. Fifty percent of the glomeruli in the sample showed active crescents without excessive scarring. There were no other immunofluorescence or electron micrograph findings were reported, establishing the diagnosis of Pauci immune glomerulonephritis. See Figure 2 for details of the renal biopsy findings.

Given active transitional malignancy, weekly steroids plus rituximab at 0.375grams/m² were started and after 3 of 4 infusions, her creatinine improved to 1.24 mg/dL from peak serum of 1.4-1.5 mg/dL in hospital. Proteinuria mildly improved from a peak urine protein to creatinine ratio of 1.5 grams protein/gram creatinine to 1.4 grams protein/gram creatinine.
**Discussion**

We present an interesting case of malignancy associated with rising ANCA titers. More unusual is the immediate drop in proteinuria noted after resection of the bladder mass. The persistence of c-ANCA titers is worrisome along with the rebound rise in proteinuria due to the concern of a relapse GPA and the possibility that the transitional cell carcinoma is still present even after bladder mass resection.

The causative link of the transitional cell malignancy in this patient’s case was likely the patient’s prior treatment with cyclophosphamide, which is associated with an increased lifetime malignancy risk.² Despite the drop in the patient’s proteinuria after removal of the bladder tumor, the recurrence of proteinuria with rising serum creatinine and c-ANCA serologies is suspicious for a GPA recurrence. Currently the patient is receiving immunosuppressive agents with Rituximab that aim to put the AAV back in remission without exacerbating the underlying transitional cell malignancy. The bladder malignancy has been resected and treated with BCG. Further imaging will monitor for recurrent bladder malignancy or metastatic disease.

**Figure 1:** plot of serum creatinine (mg/dL), proteinuria (gram protein/gram creatinine), and c-ANCA titers over time. Red arrow removal of transitional cell tumor. PR3=proteinase 3.

**Figure 2:** A)-C) fresh crescents seen on light microscopy 40x H&E and silver stains, consistent with diagnosis of Anca associated vasculitis recurrence. Red arrow removal of bladder mass, orange arrow kidney biopsy, black arrow start of rituximab treatment.

**REFERENCES**


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