

## CLINICAL VIGNETTE

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# ANCA Antibodies without ANCA Vasculitis Found on Renal Biopsy *The Importance of Obtaining Diagnostic Confirmation with Pathology Samples*

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### **Introduction**

Anti-neutrophil Cytoplasmic antibodies (ANCA) cause a spectrum of diseases known as ANCA associated vasculitis (AAV). These disease include the former eponymously named Wegener's granulomatosis (now Granulomatosis with Polyangiitis-GPA), Eosinophilic granulomatosis with polyangiitis E-GPA (formerly Churg Strauss syndrome), and microscopic polyangiitis (MPA).<sup>1</sup> These disorders generally cause pulmonary renal syndromes with hemorrhage from pulmonary arteries due to vasculitis, and crescentic and often necrotizing Pauci-immune glomerulonephritis on renal biopsies.

There are several situations where ANCA antibodies may merely be cross reacting rather than actually pathogenically involved in the disease. This has been observed in hepatitis C patients (who can sometimes get AAV) and patients with malignancies.<sup>2,3</sup> Therefore, it is important to confirm the presence of sinus granulomata, lung disease, or renal disease by biopsy to confirm the diagnosis regardless of serology findings.<sup>4,5</sup> We present an 85-year-old female with positive p-ANCA antibody titers, hematuria and mildly elevated proteinuria. She underwent renal biopsy, which did not show any signs of vasculitic disease. This case reiterates the important role of pathology in the diagnosis of AAV especially regarding renal involvement.

### **Case Report**

An 85-year-old female with past medical history of hypertension, osteoarthritis, psoriasis, and a clinical diagnosis of idiopathic pulmonary fibrosis was referred to nephrology for evaluation of ongoing microscopic hematuria. Her pulmonary fibrosis was suspected on clinical grounds with chest CT showing honeycombing and progressive restrictive pulmonary function tests.

She had apparently normal renal function with a serum creatinine of 0.4mg/dL, but a slightly decreased and an estimated glomerular filtration rate of 84 ml/min indicating very mild chronic kidney disease (CKD) stages I-II. She had ongoing hematuria with 2+ on urinalysis with increasing rbc's from 121 to 840 3 months later. Random protein to creatinine ratio was 0.2 grams protein/gram creatinine. She underwent serology testing by her rheumatologist for chronic fatigue, dyspnea, and arthralgias.

Serology demonstrated a rising (cytoplasmic) c-ANCA antibody from 1:80 in to 1:1280 in 3 months later, and a (perinuclear) p-ANCA declined from 1:640. The proteinase 3 serological test (PR3) corresponding to c-ANCA pattern was negative, but the myeloperoxidase antibody (p-ANCA corresponding pattern) was positive at 96 Units. Thus, the ANCA pattern was irregular and the antibody identified did not match the type expected with the c-ANCA predominant serology. Please see figure 1 for summary of trend of ANCA serologies, urinary red blood cells, and serum creatinine.

Due to the ongoing and rising hematuria, a renal biopsy was performed. The light microscopy specimen showed 15 glomeruli, 2 of which were obsolescent. Glomeruli had normal size and cellularity and there were no crescents. The tubulointerstitium was unremarkable. Immunofluorescence was normal and did not show any significant staining. Electron microscopy demonstrated the diffusely thin glomerular basement membranes with an average diameter of 144 nanometers. This is much less than the 250-nanometer threshold for an adult. There was no basement membrane remodeling that would suggest Alport syndrome. Thin basement membrane nephropathy was diagnosed and explained the ongoing microscopic hematuria. Figure 2 summarizes the pathological findings on renal biopsy.

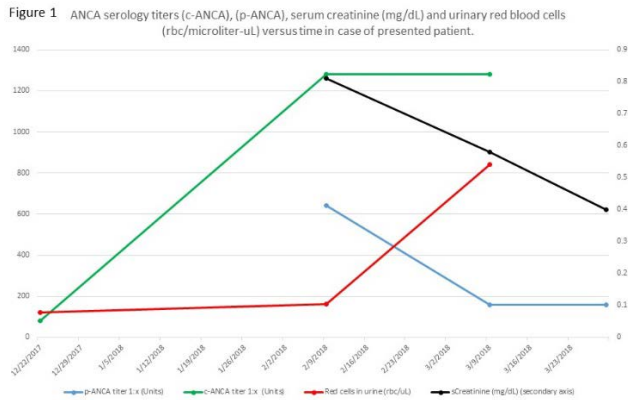
### **Discussion**

This case's positive serology was merely a cross-reactive phenomenon not indicative of AAV. The antibody demonstrated serologically was irrelevant to the observed hematuria. The more benign thin basement membrane nephropathy explained ongoing hematuria. Thus, despite hematuria and pulmonary abnormalities, the positive ANCA tests were false positive not indicative of AAV in the kidneys. Without renal involvement the lung disease was consistent with idiopathic interstitial pulmonary fibrosis.

Thin basement membrane nephropathy is a much more common and benign diagnosis than AAV. It is usually caused by abnormal glomerular basement membrane synthesis due to mutations in type IV collagen genes for alpha-3, 4 and 5 subunit chains (COL4A3, COL4A4, COL4A5). Subunits 3 and 4 are autosomal recessive mutations,<sup>6</sup> producing carrier status and thin basement membrane nephropathy in heterozygous carriers.

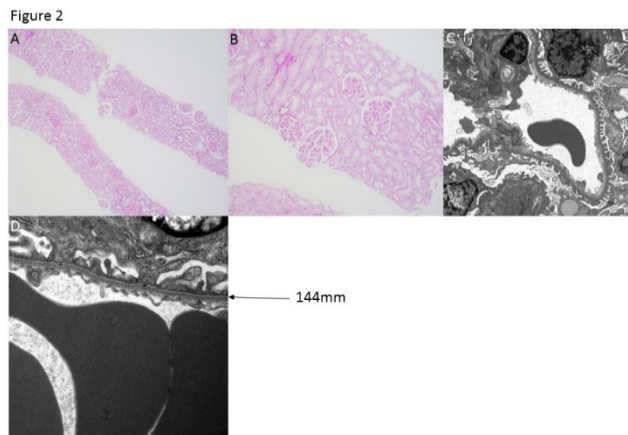
Subunit 5 results in X-linked mutations which produce Alport syndrome in affected males, or females with two mutations on both x chromosomes. Females with one x linked mutation in COL4A5, can produce thin basement membrane nephropathy in a heterozygous carrier state.<sup>7</sup>

**Figure 1:** ANCA serology titers (c-ANCA), (p-ANCA), serum creatinine (mg/dL) and urinary red blood cells (rbc/microliter-uL) versus time in case of presented patient.



**Figure 2:** renal biopsy results showing only thin basement membrane nephropathy rather than AAV in case of patient with false positive ANCA antibodies.

- A) Periodic Acid Schiff Stain (PAS) 40x low power with no scarring and normal sized glomeruli
  - B) Periodic Acid Schiff Stain (PAS) 100x high power with no scarring and normal sized and normocellular glomeruli
  - C) Electron microscopy with thin capillary loop basement membrane
  - D) Electron microscopy with thin basement membrane measured at 144 nm (<200 nm) required for diagnosis of thin basement membrane nephropathy.
- Black arrow=arrow pointing to thin basement membrane.  
Nanometer=nm.



## REFERENCES

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