Kidney Biopsy Teaching Case: Medullary Angiitis in the setting of Pauci-Immune Crescentic Glomerulonephritis

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Abstract
Almost all pathological diagnoses made from a native kidney biopsy come from careful examination of the renal cortex. In fact, a good biopsy specimen contains little medulla. It is important, however, that certain diseases have a characteristic medullary component. Medullary angiitis has histological features of interstitial hemorrhage in the medulla with an associated polymorphonuclear leukocyte infiltrate and surrounding karyorrhectic debris. These findings are primarily found in the setting of antineutrophil cytoplasmic antibody (ANCA)-associated disease. Increased awareness of this pathologic finding is needed, as these histologic findings can be misdiagnosed as interstitial nephritis alone, missing accurate diagnosis and appropriate subsequent management. Medullary angiitis identified in the setting of negative immunofluorescence is most suggestive of pauci-immune crescentic glomerulonephritis.

ABBREVIATIONS
ANCA: Antineutrophil Cytoplasmic Antibody; AAV: ANCA-Associated Vasculitis; NSAIDS: Nonsteroidal Anti-Inflammatory Drugs

INTRODUCTION
The gold standard for evaluation and proper classification of kidney disease is microscopic examination of renal tissue obtained by percutaneous needle biopsy. As noted by Pirani “the adequacy of a needle biopsy is determined not by size (length) but by the presence of renal cortex” [1]. Despite the importance of the examination of the cortex in making diagnoses, certain disease processes require close inspection of the medulla. Medullary angiitis is an uncommon finding on renal biopsies with rare descriptions in the literature [2,3]. Medullary angiitis has histological features of interstitial hemorrhage in the medulla with an associated polymorphonuclear leukocyte infiltrate and surrounding karyorrhectic debris [3,4]. The etiology of these findings is thought to be due to thrombosis of the vasa recta with subsequent medullary hemorrhage. Although medullary angiitis is occasionally seen in IgA nephropathy, and even more rarely with drug induced interstitial nephritis, it is most commonly associated with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). The rarity of this pathological finding may be due to its under-recognition as a distinct entity, particularly when the hemorrhage in the medulla is believed to be artifact, or when the inflammation seen at the corticomedullary junction is solely attributed to an acute interstitial nephritis. Increased awareness of this pathologic finding is needed, as medullary angiitis can be entirely ignored or misdiagnosed as an acute interstitial nephritis [4]. This case describes the association between medullary angiitis and systemic vasculitis with a discussion of underlying etiology.

CASE REPORT
Clinical history and initial laboratory data
A 64 year old male with history of hypertension, obesity, gout, and chronic kidney disease was admitted for evaluation of a rising creatinine. Two years prior to presentation, his baseline creatinine was 1.2-1.5mg/dL with 132 mg of albumin in a 24 hour urine collection. These findings remained stable until his creatinine increased from 1.5 to 2.2 mg/dL with 2+ hematuria over a one-month period. The patient admitted to frequent use of Nonsteroidal Anti-inflammatory Drugs (NSAIDS) for gout during that period. At that time his allopurinol was decreased from 450mg to 300 mg daily and the patient remained off NSAIDs.
Repeat labs 3 weeks later revealed a creatinine of 3.5 mg/dL with 5.2 grams protein in a 24-hour urine collection. A kidney biopsy was performed.

The biopsy contained twelve glomeruli. No glomeruli were globally sclerosed, one had a cellular crescent, two had fibrocellular crescents, and three had fibrous crescents. The glomeruli were of normal overall size and cellularity.

There was severe acute tubular injury consisting of tubular cell necrosis with sloughing and apical blebbing, tubular dilatation, and both reparative and regenerative changes. Within the medulla, there was extensive interstitial hemorrhage and leukocytoclasia of neutrophils (Figure 1). Tubular atrophy and interstitial fibrosis involved 40-50% of the cortical sample. Immunofluorescence microscopy had no significant staining for IgG, IgA, IgM, C1q, C3, albumin, fibrinogen, or kappa and lambda light chains. Electron microscopy revealed normal glomerular basement membrane thickness without deposits. There was diffuse podocyte foot process effacement involving approximately 80% of the glomerular basement membrane surface.

**Diagnosis**

Based on the kidney biopsy findings, the patient was diagnosed with pauci-immune glomerulonephritis with superimposed medullary angiitis. With this diagnosis, additional serologic studies were performed. The patient was noted to be ANCA positive with a titer of 1:320. Antigen testing was positive for myeloperoxidase. These clinical and serologic findings supported the diagnosis of pauci-immune crescentic glomerulonephritis.

**Clinical follow-up**

The induction regimen included intravenous cyclophosphamide 1000 mg with intravenous solumedrol 500 mg. He remained on prednisone 80 mg daily. After one treatment with cyclophosphamide, the creatinine decreased to 2.2 mg/dL with spot urine protein to creatinine ratio falling to 4. The prednisone was tapered, and after 6 doses of cyclophosphamide, his serum creatinine fell to 1.7 mg/dL with 2 grams of proteinuria. Due to persistent proteinuria, the patient was transitioned to intravenous rituximab 1000 mg with reduction of proteinuria to 200 mg after the second dose. The patient has received a total of four doses of rituximab and is off steroids with continued microalbuminuria and stable kidney function.

**DISCUSSION**

Medullary angiitis found on renal biopsy warranted the need for further diagnostic testing in this patient with acutely worsening renal function, and heavy NSAID use [5-7]. Histologic findings of necrotizing arteritis are variable with a reported incidence generally less than 20% in specimens with ANCA associated vasculitis [2,7,8]. Watanabe et al., originally described...
vascular damage in disease states including AAV and functions as [16]. Elevated circulating Ang-2 has been shown to reflect to the Tie2 receptor, leading to disassembly of cell-cell junctions endothelial-specific angiopoietins (Ang) like Ang-2 that binds destruction [14,15]. This process appears to be regulated by endothelial cell dysregulation and inflammation has revealed with the severity of the medullary lesions. As not all biopsies may have good cortical sampling or overt glomerulonephritis with crescents, it is important to note that medullary angiitis may be the only finding to suggest systemic vasculitis and thus lead to proper therapy. Similarly, as not all biopsy specimens include medullary tissue, this diagnosis can be elusive [9-11].

Medullary angiitis is associated with ANCA positivity, IgA nephropathy, and drug induced interstitial nephritis [2]. While NSAIDs are known to cause renal papillary necrosis, they have not been implicated in AAV. Hendrick et al., reviewed 38 patients with medullary angiitis, and 30 of these had ANCA status known. 19 of the 30 patients (67%) were identified with ANCA-associated illness [4]. Of the remaining 11 patients, 6 (20%) had IgA nephropathy and 5 (17%) had various infections treated with associated antibiotics [4].

Similar to crescentic glomerulonephritis, the finding of medullary angiitis on renal biopsy should provoke further ANCA serologic testing to determine an underlying etiology [12]. If no immunologic factor is identified (ANCA or IgA), then drug-induced etiologies should be considered. This drug-induced entity is particularly challenging to diagnose because tubulointerstitial nephritis can appear with coexistent medullary angiitis [9].

It remains unclear whether the pathogenesis of medullary angiitis is separate from AAV. Small vessel vasculitis is known to cause a leukocytoclastic vasculitis with strong dermatologic associations or even isolated cutaneous leukocytoclastic angiitis without systemic vasculitis [9]. The additional finding of necrotizing leukocytoclastic angiitis in the medullary vasa recta can be a reflection of severe disease with resultant papillary necrosis [3,9].

Watanabe et al surmised that impairment of the dual blood supply from both the vasa recta and calyceal arteries resulted in necrosis [3]. Diminished renal perfusion with relative medullary hypoxia has been proposed for the medulla specific-peritubular capillary involvement [4]. More recent investigation into endothelial cell dysregulation and inflammation has revealed complex microvascular system interplay [13]. The neutrophils stimulated by ANCA lead to endothelial cell activation and vessel destruction [14,15]. This process appears to be regulated by endothelial-specific angiopoietins (Ang) like Ang-2 that binds to the Tie2 receptor, leading to disassembly of cell-cell junctions [16]. Elevated circulating Ang-2 has been shown to reflect vascular damage in disease states including AAV and functions as a measure for the extent of endothelial cell detachment. There is a strong correlation between active AAV with renal involvement as measured by Birmingham Vasculitis Activity Score (BVAS) and Ang-2 levels [16]. These complex processes are areas of ongoing research.

In conclusion, medullary angiitis is a rare pathologic finding on renal specimens that suggests specific differential diagnostic considerations. While this finding may occur in the constellation of additional cortical tissue findings with typical glomerular involvement, the identification of medullary angiitis, particularly with negative immunofluorescence, requires shrewd clinical and pathologic awareness to arrive at the correct clinical diagnosis and provide appropriate subsequent therapy.

REFERENCES
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Cite this article