Hematuria and Proteinuria in a Patient With Recurrent Pulmonary Illnesses

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CLINICAL PRESENTATION

A 19-year-old male presented to an adult nephrology practice to establish care. He had a history of recurrent hematuria and proteinuria in the setting of upper respiratory tract illnesses. This was first noted at age 14 when he had gross hematuria associated with episodes of fever and pharyngitis two months apart. Pharyngeal swab was negative for streptococcus both times. He felt generally well otherwise. His pediatrician suspected IgA nephropathy and referred him to a pediatric nephrologist who reported the same impression and recommended a conservative management strategy. On physical examination at his initial adult nephrology visit, blood pressure was 138/87 and 130/78 and he had no edema. Laboratory studies showed serum creatinine (SCr) 1.1 mg/dL (SCr was 0.7 seven years earlier and 1.0 in the year before). Urine dipstick showed 3+ blood and 2+ protein. Urinalysis revealed hematuria (374 RBC/hpf) and 30 mg/dL protein. Spot urine microalbumin/Cr ratio (UACR) was 111 mcg/mg Cr. Medical history was significant for beta-thalassemia intermedia. Family history was positive for nephrolithiasis in his maternal grandfather.

QUESTIONS

- **What is the differential diagnosis of intermittent microscopic hematuria and proteinuria in the setting of respiratory illnesses?**
- **What studies should be included in the diagnostic evaluation of this patient?**
- **What is the clinical presentation and pathophysiologic mechanism behind this patient's disease?**
- **What are the treatment options and long-term prognosis of this disease?**

DISCUSSION

What is the differential diagnosis of intermittent microscopic hematuria and proteinuria in the setting of respiratory illnesses?

The differential diagnosis is summarized in **Box 1**. The most likely differential diagnoses in this young male with initially normal kidney function and no extra-renal disease included IgA nephropathy, postinfectious glomerulonephritis (GN), and C3 glomerulopathy (C3G). Less likely differential diagnoses included idiopathic membranoproliferative GN and atypical hemolytic uremic syndrome.

What studies should be included in the diagnostic evaluation of this case?

Laboratory workup included anti-streptolysin O, anti-DNAse B, kappa/lambda serum free light chains, serum protein electrophoresis, lactate dehydrogenase (LDH), haptoglobin, complement C3, C4, factor H, and C3 nephritic factor; all unremarkable. Kidney biopsy (**Figure 1**) showed mild mesangial hypercellularity with predominant glomerular C3 deposits. There was no glomerular staining for IgG, IgM, IgA, C1q, light chains, or fibrin. Electron microscopy revealed segmental mesangial, subepithelial, and subendothelial immune-type electron dense deposits with segmental duplication of glomerular basement membranes. No "hump-like" subepithelial deposits were identified. These findings were consistent with C3 glomerulonephritis (C3GN), a subtype of C3G.

Family history was remarkable for Cypriot ancestry on his paternal side and Greek ancestry on his maternal side, raising concern for complement Factor H-related protein 5 (CFHR5) nephropathy. CFHR5 nephropathy is an autosomal dominant disease with >90% penetrance and is endemic in Cyprus, where the carrier rate for the fusion gene is ~1 in 6500 and over 100 persons are affected.[2] Genetic testing confirmed the presence of the *CFHR5-CFHR5* fusion gene.

The clinical and histological features of CFHR5 nephropathy bear a striking similarity to IgA nephropathy (IgAN), although in CFHR5 nephropathy no IgA deposition is seen. Kidney biopsy and genetic testing are central to its diagnosis and to distinguish it from IgAN.

What is the clinical presentation and pathophysiologic mechanism behind this patient's disease?

The *CFHR5-CFHR5* fusion gene found in CFHR5 nephropathy encodes an elongated version of the CFHR5 protein, which acts as a competitive inhibitor of factor H, resulting in complement dysregulation.[2-4] CFHR5 nephropathy typically presents with microscopic hematuria, almost always with respiratory infections; 25-50% of patients have macroscopic hematuria. Proteinuria is typically mild (<1 g/day) and only present after kidney function has become impaired.[1]

What are the treatment options and long-term prognosis of this disease?

There is no proven treatment for CFHR5 nephropathy. Disease progression correlates with infectious episodes, and tonsillectomy has shown occasional good long-term results based on anecdotal and uncontrolled reports.[5] Conventional immunosuppressive agents are not beneficial.[1] Plasma exchange during episodes of macroscopic hematuria and acute kidney dysfunction has

shown short-term benefit. It is unknown whether eculizumab is beneficial.[1] Progressive deterioration of kidney function occurs in over 80% of males (but only a small proportion of females) and leads to kidney failure usually between 30-70 years of age.[1] Kidney transplantation provides good outcomes, but the disease does recur consistent with its genetic etiology.[1]

This patient was started on lisinopril 10 mg daily. Home blood pressures have remained stable. Over the ensuing several months, creatinine ranged from 1.5 to 1.9 mg/dL and UPCR has ranged from 610 to 810 mg/g Cr (**Table 1**). Continued supportive care is planned.

FINAL DIAGNOSIS

Complement Factor H-related protein 5 (CFHR5) nephropathy causing C3GN due to a heterozygous mutation in the *CFHR5* gene.

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Patient Protections: The authors declare that they have obtained consent from the patient reported in this article for publication of the information about him that appears within this Quiz.

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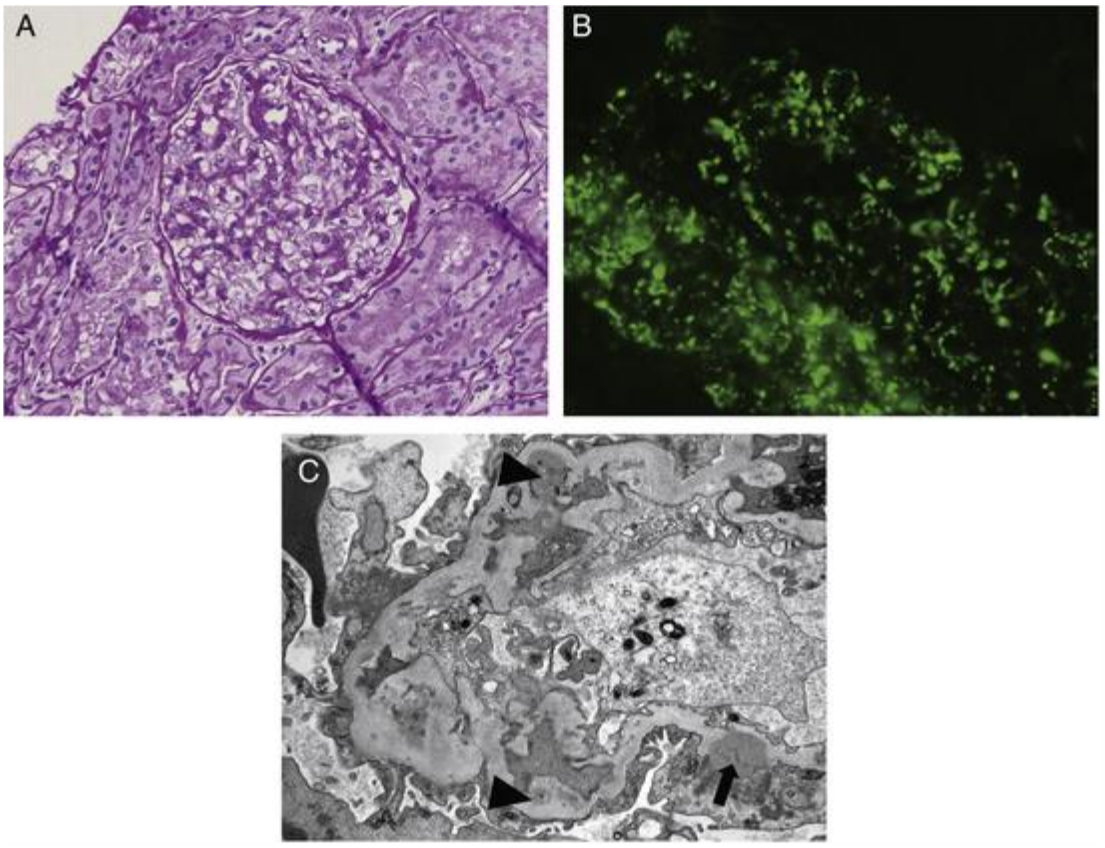

Figure 1. Renal biopsy pathology

1A. Glomerulus shows mild mesangial hypercellularity and patent capillary lumina. (Periodic acid-Schiff; x200)

1B. Immunofluorescence microscopy shows a glomerulus with global granular mesangial and capillary wall staining for C3. (x400)

1C. Electron photomicrograph shows duplication of glomerular basement membrane with a few intramembranous electron dense deposits (arrow-heads). A single subepithelial electron dense deposit is also seen (arrow).

Table 1. Kidney function and proteinuria over time

Time relative to presentation to adult nephrology	Creatinine (mg/dL)	Urine protein/Cr ratio (mg/g Cr)	Urine albumin/Cr ratio (mcg/mg Cr)
–7 yrs	0.7		
–1 yr	1.0		
Time of presentation	1.10		111
+1 mo	1.29		
+5 mos	1.44	1000	
+7 mos	1.58	580	
+12 mos	1.62	510	
+15 mos	1.89	610	
+16 mos	1.51		
+17 mos	1.66	810	
+19 mos	1.83		

Box 1. Differential diagnosis of intermittent hematuria and proteinuria in the setting of respiratory illnesses

- IgA nephropathy (IgAN) and IgA vasculitis
- Post-infectious glomerulonephritis (PIGN)
- C3 glomerulopathy (C3G)
    - C3 glomerulonephitis (C3GN)
        - Complement Factor H-related protein 5 (CFHR5) nephropathy
    - Dense deposit disease (DDD)
- Idiopathic membranoproliferative glomerulonephritis (MPGN)
- Atypical hemolytic uremic syndrome (HUS)