CLINICAL VIGNETTE

A Red Herring: A Case of Microscopic Hematuria

Sharad Patel, M.D, Huma Hasnain, M.D, Ajoe Katoor

Introduction

The evaluation of new-onset microscopic hematuria in an adult patient involves the distinction of etiology as glomerular versus non-glomerular. This distinction is vital, given the markedly different evaluation and management course. Microscopic hematuria accompanied by significant proteinuria is suggestive of glomerular bleeding. We present a 50-year-old female with a past medical history of Systemic Lupus Erythematosis (SLE) who presents with new-onset of microscopic hematuria with a spurious presentation of concurrent nephrotic-range proteinuria secondary to urinary RBC hemolysis.

Case

A 50-year-old woman with SLE and Connective Tissue Disease – Associated Interstitial Lung Disease (CT-ILD) on chronic immunosuppressive agents actively awaiting lung transplant, presented to the emergency department with worsening shortness of breath. On initial examination the patient was tachypneic and hypoxemic at 88% despite 15 Liters of high flow oxygen. She was admitted to the MICU and intubated. Her status on the on the lung transplant list was immediately upgraded. A Chest CT was remarkable for severe chronic bilateral lung fibrosis with new interstitial infiltrates likely consistent with pneumonia. Despite the patient's long history of rheumatological diseases there was no prior renal involvement. The patient's baseline serum creatinine was stable at 1.0 with bland urine sediments while on an immunosuppressive regimen of hydroxychloroquine, prednisone and azathioprine.

One week after admission, the patient remained intubated and required 80% FIO2 to maintain oxygen saturations above 88%. On hospital day 7, AST and ALT levels increased to 128 and 142 U/L (8-60 U/L) respectively, and the azathioprine was discontinued given concern of drug-induced hepatotoxicity. On hospital day 10 a routine Urinalysis noted 4 + Blood, 3+ proteinuria and 4+ RBC's. Of note a urinalysis from an outpatient visit 2 months prior had noted 1+ protein, and no microscopic hematuria. On day 10 a spot urine protein/creatinine ratio was 4.2 grams with Cr remaining stable at 1.0 mg/dl. The urine specimens were obtained from a foley catheter which was thought to account for the new-onset of microscopic hematuria but not the nephrotic range proteinuria. Nephrology was consulted on hospital day 10 for concern of new-onset glomerulonephritis secondary to SLE. Distinguishing the etiology of microscopic hematuria in the setting of proteinuria as a new diagnosis of lupus-nephritis could downgrade her from the lung transplant list, with potentially fatal outcome given her tenuous pulmonary status.

Microscopic analysis of the RBC's was inconclusive with no evidence of dysmorphic red cells typically suggestive of glomerular etiology. Serological studies such as DS-DNA and c3 and c4 complements levels were abnormal but remained consistent with previous values. Despite the innocuous nephritis work up thus far, Lupus nephritis remained high on the differential given the past medical history of SLE and recent discontinuation of her azathioprine. Given the need for a definitive diagnosis for purpose of lung transplant listing, a kidney biopsy was ordered. The biopsy was scheduled for hospital day 12. However, prior to kidney biopsy, Nephrology recommended a repeat the UA after removal of the foley catheter. The repeat UA showed 1+ blood, 1+ RBCs and quite surprisingly decreased 1+ proteinuria, with a repeat urine protein/creatinine ratio of 0.86 grams.

The decrease in proteinuria was perplexing but in hindsight we noted that the nephrotic range proteinuria only occurred in the setting of gross hematuria with urine gathered from the foley bag. We decided to order a urine protein electrophoresis (UPEP) in order to identify the predominant protein from the prior nephrotic range urine sample. The UPEP had a Beta spike rather than an expected albumin spike in true nephrotic range proteinuria. Based upon the Beta spike it was inferred that the predominant protein on the previous quantification of protein was hemoglobin from lysed RBC's. The correlation between the elevated protein quantification, low urine specific gravities, and the RBC load was not lost. Tapp et el had previously noted that RBC lysis increases in the setting of old RBC's. Given that the initial UA samples were retrieved from a foley catheter bag it was likely that these RBC's would be more predisposed to lysis.

We intended to cancel the renal biopsy but given the critical importance, the lung transplantation committee requested biopsy. The biopsy did not show active glomerulonephritis/immune-complex deposition but instead only minimal interstitial fibrosis. The patient was placed back as priority status for lung transplantation.

Labs

Urine Analysis				
Day	Specific Gravity	RBC	Protein	Total Protein/Cr ratio (grams)
1	1.033	1+	1+	Not available
2	1.009	4+	3+	3.8
3	1.008	4+	3+	4.1
4	1.019	1+	1+	0.86

Discussion

Evaluation of microscopic hematuria in a patient should involve clues from history, classifying as glomerular versus non-glomerular etiology and either as transient or persistent[1]. Presence of urinary dysmorphic RBCs suggests glomerular etiology even though a slight overlap can be present between renal and non-renal pathologies[2]. Accurate assessment of morphology of RBCs requires the use of phase contrast microscope which may not be readily available.

In our patient, microscopic hematuria in the setting of proteinuria with a background of SLE created a high suspicion of glomerular renal disease. It is considered to be "common knowledge" to have proteinuria in the presence of gross hematuria but the mechanism is rarely verbalized. Furthermore, there is not much in the literature that provides a mechanistic explanation of spurious proteinuria in the setting of gross hematuria.

Tapp et al reported RBC lysis contributing to spurious proteinuria[3]. They simulated hematuria by adding blood into urine samples of varying osmolality's. Gross hematuria often resulted in protein in urine. This was more pronounced when urine was hypotonic with fluid shift into the cell leading to lysis. The study demonstrated that dysmorphic old RBCs are more susceptible to lysis, especially in combination with dilute urine. The amount of protein found in the urine contaminated with blood is thus a function of the osmolality of urine, cell morphology as well as the amount of blood in the urine.

Conclusion

Evaluation of microscopic hematuria in the setting of proteinuria can be guided by non-invasive evaluation with UPEP to further evaluate the distribution of proteinuria. Large amounts of urinary hemoglobin will lead to a Beta spike on the UPEP rather than the expected albumin spike. Accurate determination of the distribution of proteinuria can act as a screening tool to rule out 'spurious proteinuria' due to rbc lysis and possibly prevent an unnecessary intervention such as renal biopsy. In most cases we would have been able to avoid biopsy given the UPEP results but given the gravity a renal biopsy was obtained.

REFERENCES

1. **Schramek P, Schuster FX, Georgopoulos M, Porpaczy P, Maier M**. Value of urinary erythrocyte morphology in assessment of symptomless microhaematuria. *Lancet*. 1989 Dec 2;2(8675):1316-9. PubMed PMID: 2574263.
2. **Pollock C, Liu PL, György AZ, Grigg R, Gallery ED, Caterson R, Ibels L, Mahony J, Waugh D**. Dysmorphism of urinary red blood cells--value in diagnosis. *Kidney Int*. 1989 Dec;36(6):1045-9. PubMed PMID: 2689749.
3. **Tapp DC, Copley JB**. Effect of red blood cell lysis on protein quantitation in hematuric states. *Am J Nephrol*. 1988;8(3):190-3. PubMed PMID: 3239591.

Submitted on July 25, 2014