Non-nephronal hematuria misdiagnosed as C1q nephropathy: Look before you leap

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ABSTRACT

A 19-year-old male presented with persistent macroscopic hematuria for last 3 months. On initial evaluation, he was found to have minimal proteinuria, normal renal function, and normal complement with negative lupus serology. Light microscopy, immunofluorescence and electron microscopy of renal tissue confirmed the presence of C1q nephropathy. Because of poor response to immunosuppressive agent (prednisolone and mycophenolate mofetil), passage of urinary clot once and vexing persistent macroscopic hematuria, alternative diagnosis was considered. Cystourethroscopy showed urethritis of prostatic urethra. Immunosuppressives were stopped and doxycycline started to which hematuria responded dramatically. This case report illustrates that hematuria in this patient was because of undiagnosed urethritis rather than incidental C1q nephropathy.

Key words: C1q nephropathy, persistent macroscopic hematuria, urethritis

Introduction

Isolated macrohematuria as a sole presentation in a young patient in a nephrological clinic is usually due to Ig-A nephropathy, thin basement membrane disease or Alports syndrome provided hematuria is truly glomerular or nephronal.[1,2] A phase contrast microscopy of freshly voided sample, despite poor sensitivity compared to automated urine flow cytometry, could be a great help to narrow the differential diagnosis wherever available lest one investigates nonglomerular hematuria as a glomerular disease.[3,4] We present an interesting case of misdiagnosed hematuria of unsuspected aetiology.

Case Report

A 19-year-old male presented with red coloured urine for 3 months. There was no preceding history suggestive of lower urinary symptoms or trauma. No history of fever, rash, oliguria, joint pain, or arthralgia was elicited. Hematuria was painless. There was no family history suggestive of renal disease. He had no visual deficit and hearing impairment. There was no nephritic or nephrotic illnesses in past. He denied any possibility of sexually transmitted infection.

General examination was found to be unremarkable with no pallor, pedal edema, and his blood pressure was 120/80 mmHg. Laboratory evaluation showed Hb-15.8 gm/dl, TLC-12800/cmm, RBC-4.5 million/cmm, platelet-2 lakh/cmm, PT-29.6 second, APTT-35 second, BUN-7 mg/dl, serum sodium-138 meq/l, serum creatinine -0.93 mg/dl, total protein 6.5 gm/dl, and albumin-4.1 gm/dl. Lupus serology, both ANA (biochip indirect immunofluorescence, dilution-1, 100) and ds DNA were negative. Urine light microscopy examination showed plenty of RBC/hpf with no cast. Variable proteinuria was seen on two occasions (urine spot protein/creatinine ratio 0.4 and 1.9). He had normal serum complement C3/C4 level.

The ultrasound examination of abdomen was normal with normal-sized kidney, normal echogenicity, and maintained corticomedullary differentiation. Because of persistent gross hematuria a possibility of Ig-A nephropathy was considered and percutaneous renal biopsy was done

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at a peripheral centre. Kidney biopsy was reported to be C1q nephropathy [normal histology on light microscopy and C1q deposits on immunofluorescence (IF)]. He was advised to take deflazocort (60 mg/day). Even after taking it for 4 weeks, there was no response and the patient was referred for reassessment. Mycophenolate mofetil 2 gm/day was added to the regimen of immunosuppression with prednisolone (60 mg) substituted for deflazocort therapy in the hope of better response. A month later as macrohematuria still persisted; a repeat renal biopsy was decided as the presentation of persistent macrohematuria was considered atypical.

Second renal biopsy showed normal glomeruli on light microscopy with no increase in cellularity, basement membrane thickening, or segmental sclerosis. The tubules, vessels, and interstitium were unremarkable [Figure 1a and b]. IF study showed significant mesangial deposits of C1q with minimal deposits of IgG and IgM [Figure 2]. Electron microscopy showed normal cellularity, patent capillaries, and basement membrane of normal thickness with intact foot processes. Many electron-dense deposits were seen in the mesangium and few in the subendothelial region [Figure 3] thereby fulfilling all the histological criteria of C1q nephropathy. After completing 4 weeks of treatment with prednisolone/MMF patient complained of no improvement in his red coloured urine. On detailed enquiry, he admitted to passing some clots recently. Repeat urine light microscopy of freshly voided sample by the nephrologist revealed hematuria to be isomorphic rather than dysmorphic that was confirmed to be the case with phase contrast microscopy. Mid stream urine culture was sterile. On further evaluation by cystourethroscopy, prostatic urethra was noted to be markedly congested suggestive of prostatic urethritis. In view of sterile urine culture, he was given an empirical therapeutic trial with 2-week course of doxycycline. There was dramatic symptomatic improvement with urine becoming clear and repeat urine examination becoming completely normal with no hematuria or proteinuria for the first time 5 months from its onset.

Discussion

Ours is an interesting case of missed urological cause of hematuria that was masquerading as C1q nephropathy. It goes without saying that any case of gross hematuria without footprints of renal parenchymal involvement mandates a detailed urological work up rather than going ahead with kidney biopsy that nephrologists are so used to.

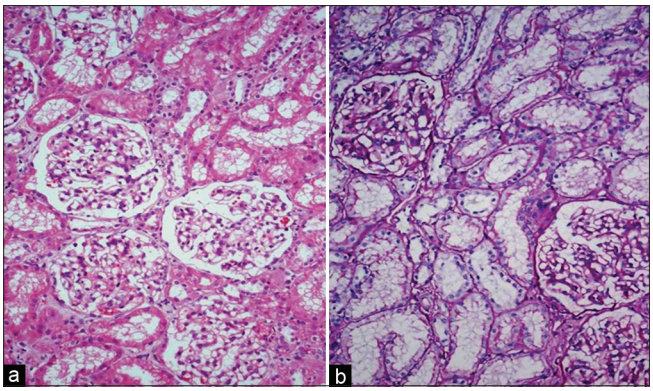

Figure 1a and b: H and E stained section in the left panel and PAS stained section in the right panel showing normal glomeruli, tubules, and interstitium

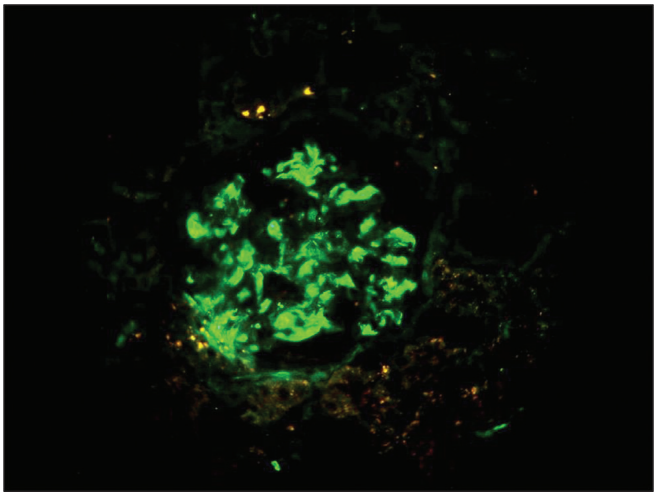

Figure 2: Significant mesangial deposits of C1q on immuno-fluorescence stain (FITC labeled C1q ×400)

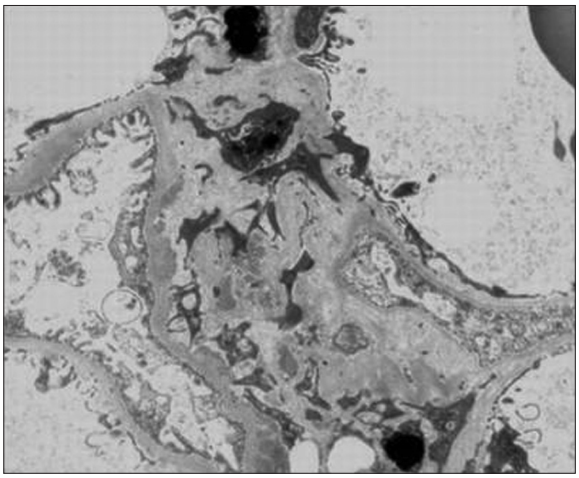

Figure 3: Ultrastructure showing electro dense deposits in the mesangium with few subendothelial deposits (×25 000)

The identification of the glomeruli as the source of bleeding is important both prognostically and to optimize the subsequent evaluation.[3] In particular, patients with clear evidence of glomerular hematuria do not need to be evaluated for potentially serious

urologic disease. Distinctive features of glomerular hematuria include red cell casts, protein excretion exceeding 500 mg/day at a time when there is no gross bleeding, a dysmorphic appearance of most (>80%) red cells (particularly if >5% acanthocytes), brown to cola-colored urine with gross hematuria and lower mean corpuscular volume (MCV) of RBC based on coulter analysis of urine.[3-5] Although helpful if present, the absence of these findings does not exclude glomerular disease. When persistent hematuria is essentially the only manifestation of glomerular disease, one of three disorders is most likely namely Ig-A nephropathy, Alport syndrome, and thin basement membrane nephropathy (gross hematuria unusual). One of these three conditions is present in more than one-half of adults with isolated hematuria and a negative radiologic and cystoscopic evaluation who are referred for further evaluation.[2] In our case, we missed the nonglomerular cause of hematuria as attention was not paid to urine erythrocyte morphology in urine microscopy.

C1q nephropathy was first described by Jennette and Hipp[6] in 1985 for biopsies exhibiting dominant or codominant mesangial staining for C1q in glomeruli and confirmation of such mesangial deposits by electron microscopy in patients with no clinical or serological features of systemic lupus erythematosus or in the absence of the membranoproliferative glomerulonephritis (MPGN) pattern.[7] It is an uncommon glomerular disease that is becoming established as an independent disease over 25 years time from its first report.[8-10] In clinicopathological studies, C1q nephropathy is characterized by its onset in older children and young adults with severe proteinuria or nephrotic syndrome with resistance to steroid treatment, frequent recurrence, and poor long-term prognosis.[9-11] Serological examination reveals no antinuclear antibodies or complement abnormalities. Histolopathological findings range from podocytopathy with MCD/FSGS variant and a typical immune complex glomerulonephritis variant (no glomerular lesion, mesangioproliferative, MPGN like, membranous nephropathy or focal segmental MN) that could be primary or related to virus infections like HIV/BK virus and CMV.[11] According to Vizjak *et al*., C1q nephropathy can rarely be seen in clinically healthy people.[10] It was seen not only in two kidney donors with normal urine examination but C1q containing immune deposits were also seen in their study in 19.4% of patients with clinically and histopathologically proven hypertensive nephrosclerosis, tubulointerstitial nephritis, Hantavirus nephropathy, cystic renal disease, and thin basement membrane nephropathy, most likely as an unrelated concomitant condition. It is not clear whether these deposits have any significance or merely immune deposits of uncertain significance similar to IgA deposits being seen as an incidental finding in kidney from healthy transplant donors which questions the validity of C1q nephropathy as a distinct clinicopathologic entity.[8,10] Therefore, the problems in establishing a disease entity of C1q are many. There is no clarity about aetiopathogenesis of this entity. The clinical utility of diagnosing C1q is still not established and it is a disease of exclusion. Moreover, C1q staining is now becoming a routine part of renal biopsy work up at many centers with the result that many cases of surprise diagnosis of C1q coming up which at times poses many therapeutic dilemmas as was seen in this case.

The C1q nephropathy was an incidental finding because macrohematuria was not from dysmorphic erythrocyturia that persisted despite immunosuppressive treatment and responded dramatically to doxycycline as the source of isomorphic hematuria was urethritis rather than kidney. The presence of C1q in this case could well represent a benign lesion like some report of Ig-A deposit in normal kidney or could be first hit of the two hit hypothesis of many immune complex diseases still not manifest. This case illustrates the importance of basic urine analysis by treating physician to circumvent unnecessary investigations cum treatment. The lesson we learnt from this real life situation was of missing the urological diagnosis of hematuria that resulted in potentially harmful treatment approaches that should be avoided by adhering to basics of hematuria work up.

References

1. Tryggvason K, Patrakka J. Thin basement membrane nephropathy. J Am Soc Nephrol 2006;17:813-22.
2. Topham PS, Harper SJ, Furness PN, Harris KP, Walls J, Feehally J. Glomerular disease as a cause of isolated microscopic haematuria. Q J Med 1994;87:329-35.
3. Fairley KF, Birch DF. Hematuria: A simple method for identifying glomerular bleeding. Kidney Int 1982; 21:105-8.
4. Apeland T. Flow cytometry of urinary erythrocytes for evaluating the source of haematuria. Scand J Urol Nephrol 1995;29:33-7.
5. Fogazzi GB, Edefonti A, Garigali G, Giani M, Zolin A, Raimondi S, *et al.* Urine erythrocyte morphology in patients with microscopic haematuria caused by a glomerulopathy. Pediatr Nephrol 2008;23:1093-100.
6. Jennette JC, Hipp CG. C1q nephropathy: A distinct pathologic entity usually causing nephrotic syndrome. Am J Kidney Dis 1985;6:103-10.
7. Jennette JC, Hipp CG. Immunohistopathologic evaluation of C1q in 800 renal biopsy specimens. Am J Clin Pathol 1985;83:415-20.
8. Markowitz GS, Schwimmer JA, Stokes MB, Nasr S, Seigle RL, Valeri AM, *et al.* C1q nephropathy: A variant of focal segmental glomerulosclerosis. Kidney Int 2003;64:1232-40.
9. Iskandar SS, Browning MC, Lorentz WB. C1q nephropathy: A pediatric clinicopathologic study. Am J Kidney Dis 1991;18:459-65.
10. Vizjak A, Ferluga D, Rozic M, Hvala A, Lindic J, Levart TK,

et al. Pathology, clinical presentations, and outcomes of C1q nephropathy. J Am Soc Nephrol 2008;19:2237-44.
11. Mii A, Shimizu A, Masuda Y, Fujita E, Aki K, Ishizaki M, *et al*. Current status and issues of C1q nephropathy. Clin Exp Nephrol 2009;13:263-74.

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