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Case report

HEMATURIA IN HEMOPHILIA: WHAT DO WE KNOW? A CHALLENGING CASE STUDY AND LITERATURE REVIEW

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ABSTRACT

Hemophilia is a genetically determined bleeding disorder, which, if not properly managed, can cause lifelong disabilities. Hemorrhages in the joints and soft tissues are largely studied. On the other hand, there is limited literature investigating renal dysfunction for these disorders. Hematuria is a recognized complication of hemophilia. While it is generally considered benign, hematuria can lead to chronic renal damage. We report the case of a 12 year-old male affected by hemophilia B, who was evaluated for gross hematuria. A literature review is also included where we identify some unanswered questions.

1. Case report

A 12-year-old male with a severe FIX deficiency (FIX < 1 IU/dl or < 1 % of normal) was admitted to the pediatric clinic at Catania University, Italy, with a 2-week history of asymptomatic gross hematuria without clots. He received a diagnosis of HB at the age of 2.5 years, and is currently in treated with Benefix®. Upon admission, the physical examination revealed no abnormal signs. Blood pressure was 105/70mmHg. Laboratory blood tests revealed a normal activated partial thromboplastin time (34 sec, normal value 28-40 sec), prothrombin time-international normalized ratio 1.2, platelet count 500.000 per mm^3 and serum creatinine level (0,7mg/dL) within normal ranges for his age; eGFR (Bedside Schwartz Formula) 79.65mL/min/1.73 m^2

Urinalysis was normal, except for the gross hematuria and high proteinuria, which lead to suspicion of a nephrotic syndrome, even if, clinically, there were no signs of a nephrotic syndrome.

Other urinary parameters: ph 6, density 1005, no leukocytes or glucose. At the first urinary test, exams revealed U-proteins 174.9 mg/dL and U-creatinin 35.6 mg/dL: thus, urine protein/creatinine ratio was 4913 mg/g, 4.9g/day estimated. The next day, the first 24-hour urine collection started with these results: albumin in urine was 986 mg/24h (normal value <30); proteins in urine were 3483 mg/24h (normal value 40-150); creatinine in urine was 1133mg/24h (normal value 980-2200).

Laboratory tests revealed normal values of albumin, normal serum proteins, normal C3 and C4 and normal triglycerides and cholesterol. The child received regular doses of IX recombinant factor (70 mg/kg, once for week i.v.). The parents referred that the child had not skipped a dose of medication, had not had any hemorrhagic episodes, and had not had any recent viral or bacterial infections or recent trauma.

We treated the child with hydration according to Holliday-Segard nomogram (4 ml/kg/h for the 1st 10 kg, 2 ml/kg/h for the 2nd 10 kg, 1 ml/kg/h for the remainder) and bed rest, as recommended by guidelines.

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The first laboratory dosing of FIX level was above 8%. Microscopic examination of the urinary sediment revealed mixed glomerular hematuria (dysmorphic red blood cells < 40%, acanthocytes > 5%; there was no possibility to study urinary cylinders for gross hematuria) as glomerular damage. For this reason, an abdominal Ultrasound was performed, which was negative, and computed tomography with contrast demonstrated that his right pyelocaliceal cavity and bladder were filled with blood clots (Figure 1 and 2). This was treated conservatively with IX recombinant factor (70UL/kg iv, 1 administration for a week) and hydration, monitoring hemoglobin values, albumin and lipid profile, and FIX dosing. Four weeks after the first hematuria episode, the child referred a pain typical of renal colic, more intense between the right ribs and hip, and nausea. The acute pain was treated with Paracetamol. After several hours, blood clots appeared in the urine. After that, no gross macrohematuria was evident. Upon urinary examination, no presence of microscopic red blood cells was noticed. The Farley test revealed no dysmorphic cells. In the last 24 hours of urine collection, albumin was 4.7 mg/24hours (0.0-30 normal range), and proteins were 157 mg/24hours (40-150 normal range).

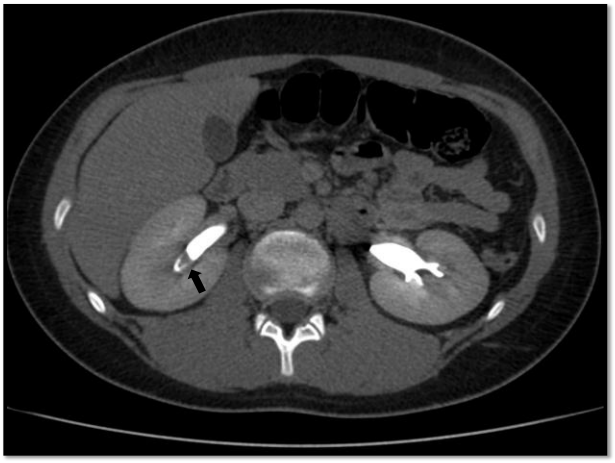

Figure 1. Clot in right pyelocaliceal cavity, indicated by black arrow.

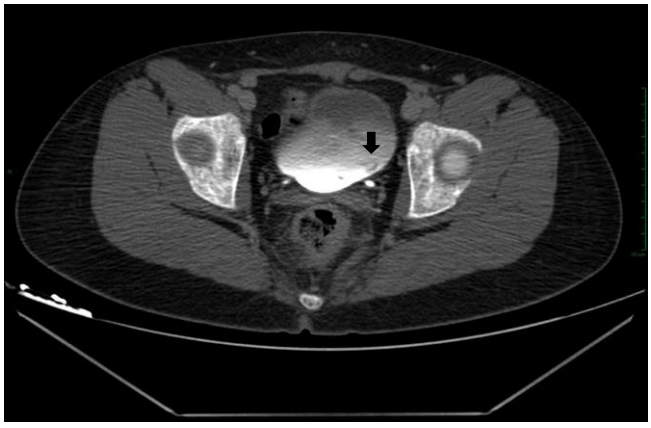

Figure 2. Clot in the bladder, urographic phase. The clot is indicated by a black arrow.

2. Discussion

HB is a hereditary hemorrhagic disorder resulting from a congenital deficit of FIX. The disease is categorized by mild hemophilia (5%-50% of FIX), moderate hemophilia (1% - 5% of FIX) and severe hemophilia (< 1% of FIX).[1] According to the official guidelines, the goal of dosing is to maintain FIX level above 1 to 2 percent, mainly converting the affected subject from a severe to a moderate hemophilia phenotype.[1] The child in our case study was in treatment with prophylactic FIX (Benefix®) and the FIX-dosing evaluation revealed an optimal prophylactic value (above 8% of fixed dosing).

The causal onset of hematuria in HA or HB is often unclear, as in our experience. It can be attributable to the underlying coagulation deficiency. In general, the etiology of hematuria is broad, ranging from benign causes such as nephrolithiasis, cystitis, prostatitis to potentially life-threatening malignancies, including malignant renal cell carcinoma, bladder cancer, nephrolithiasis bladder cancer, renal cell cancer, and prostate cancer. Severe hematuria has rarely been reported in hemophilia, and no one describes the presence of massive proteinuria (> 5,5 gr in 24 hours) as exhibited in our case study presented herein. Viteri and Reid-Adam reported that coagulation disorders manifest in children with hematuria in absence of proteinuria.[2] In our case, the suspicion of nephrotic syndrome was in contrast with the clinical presentation and serum protein values, and the elevated transient proteinuria could be indicated as nephrotic range proteinuria. On the other hand, the analysis of the urinary sediment described the presence of acanthocytes, a typical sign of glomerular damage. Regarding our case, we presumed that proteinuria in a nephrotic range could be explained by two different hypotheses, probably not exhaustively on just one: in minor part, by the disruption of the red cells containing hemoglobin's protein, in second and major part by an initial glomerular damage. A review of Kanfer explains the possible role of coagulation in glomerular injury[3]: fibrin may occlude glomerular capillaries, by attracting macrophages or by direct cytotoxicity to mesangial cells. For example, in rats, studies show fibrin deposits contribute to the progressive renal lesions and chronic renal failure, in which anticoagulant therapy has a beneficial effect. Thus fibrin, as an important component of blood clots, can contribute to glomerular damage. Free heme is potentially toxic: it can cause renal injury inducing chemokines by factor NF-κB. Additionally, in chronic kidney disease free iron has a role in oxidative stress, accelerating the damage of lipids, proteins, and DNA. Therefore, the renal function should be monitored during the entire clinical course. Similarly, FIX inhibitors can cause nephrotic syndrome for immune tolerance induction. Recently, Qvigstad et al. reported a study about the association between recombinant factors and macroscopic hematuria.[4]

Our strategy consisted in conservative treatment. Historically, hematuria in subjects with hemophilia is considered benign and usually responds to hydration, bed rest, and infusions of factor concentrate. However, in cases where conservative measures fail, how to handle the management is still not well defined. Additionally, we have noted the lack of a temporal-definition of refractory hematuria and of an optimal therapy to apply in these cases.

Kaye et al. reported a study about the role of epsilon aminocaproic acid in the case of refractory hematuria in children with hematological disorders. In the study, 1 out of 4 reported children was affected by hemophilia A and 4-weeks-hematuria: after the administration of epsilon aminocaproic acid, there was a cessation of hematuria within 7 days.[5] Kelsey et al. reported a case of a 35-year-old individual with hemophilia B and gross hematuria, resolved by the use of stored plasma to maintain the FIX levels at 60 percent.[6] Washino et al. described the case of 60-year-old individual with hemophilia A and gross hematuria: after the failure of conservative therapies, clot evacuation by vesicoclysis, continuous bladder irrigation with normal saline and intravesical instillation, at the end cystectomy was carried out.[7]

Gomperts et al. described a 15-year-old boy with moderate hemophilia, who required renal transplantation: in his history, he showed persistent hematuria at 5 years of age, followed by proteinuria and anemia at age 13, and subsequently hemodialysis and renal transplantation.[8]

Even though hematuria in hemophilia is usually considered a benign condition, data in the literature are different and sometimes in contrast. Forbes and Prentice reported that macroscopic hematuria is associated with a reduction in renal function.[9] In the cohort of Kulkarni et al., kidney bleeding was associated with chronic renal disorder.[10]

Heavy hematuria is a significant problem in hemophilic subjects. In the literature there is a lack of data about the management of refractory hematuria which is a rare but possible event. Further studies are required to point out the correct management in case of persistent hematuria with possible renal dysfunction

This case-report is an example of a close relationship between HB, hematuria and glomerular damage.

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