abstract

Two sisters, aged 15 and 13 years, had previous epithelioid angiomyolipoma of the kidney and suspected thin basement membrane disease, respectively. They presented with 2 years of gross hematuria and new-onset heavy proteinuria. Extensive investigations failed to find an overt cause of their urinary manifestations. The diagnosis of child abuse in a medical setting was confirmed by DNA short tandem repeats analysis, which are the first documented cases in which factitious hematuria was thus diagnosed. Complex forms of child abuse in a medical setting may require forensic tests such as DNA short tandem repeats analysis for diagnosis. Pediatrics 2012;130:e224–e229

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KEY WORDS

child abuse in a medical setting, DNA short tandem repeats, hematuria, Munchausen syndrome by proxy

ABBREVIATIONS

CAMS—child abuse in a medical setting
HPF—high power field
Ig—immunoglobulin
RBC—red blood cell
STRs—short tandem repeats
TMBD—thin basement membrane disease

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Macroscopic hematuria in children has an estimated incidence of 1.3 per 1000. Blood in the urine can come from the kidneys or anywhere in the urinary tract. Some potential etiologies of gross hematuria in children include poststreptococcal glomerulonephritis, immunoglobulin (Ig) A nephropathy, hypercalciuria, sickle cell trait, thin basement membrane disease (TBMD), Alport hereditary nephritis, calculi, and vascular or bladder pathology. It can be diagnosed with history, laboratory tests, kidney biopsy, radiologic imaging, or cystoscopy. Factitious hematuria is a rare cause of hematuria in pediatric patients. If the cause of the hematuria remains unclear after extensive investigations, child abuse in a medical setting (CAMS) should also be considered. Herein, we report on 2 sisters who were known to have documented underlying genitourinary lesions with persistent gross hematuria and new-onset heavy proteinuria; CAMS was confirmed by DNA short tandem repeats (STRs).

CASES 1 AND 2

Two sisters, aged 13 and 15 years, presented with gross hematuria of 3 years’ duration. Their mother was the main caregiver, and their father had been absent from every outpatient visit and admission. The older sister (Case 1) had a history of generalized tonic-clonic seizures, which had been controlled with antiepileptic drugs for 5 years. She had begun to notice gross hematuria and dysuria nearly 8 months before her first admission to our hospital 3 years earlier. CT of her abdomen showed a 3.1 × 1.7 cm non-fat-containing mass extending from the midpole of the left kidney. No cutaneous lesions such as facial angiofibromas, ash leaf macules, or shagreen patches were noted. MRI of her brain did not show any evidence of subependymal nodules. She was treated by partial nephrectomy with a pathologic diagnosis consistent with epithelioid angiomyolipoma. Convalescence was uneventful; however, she had recurrent gross hematuria and new-onset proteinuria at 4 months’ postoperation. Blood chemistry, renal function, serum complement, IgA, IgG, and IgM concentrations, antistreptolysin O titer, coagulation profile, antinuclear antibodies, anti-double-strand DNA, rheumatoid factor, and anti-neutrophil cytoplasmic antibody were all within normal range. Ninety percent of urinary red blood cells (RBCs) were of normal morphology. Urinary protein excretion ranged from 0.37 to 2.67 g per day. Other diagnostic modalities, including urinary cytology, cystoscopy, intravenous pyelography, angiography, and a kidney biopsy were all normal. Surveillance abdominal ultrasound and CT were performed every 6 months after surgery; they did not reveal any renal, ureteric, or bladder pathology. Gross hematuria combined with proteinuria was still present at the last visit, 3 years after her first admission. Collect clean-catch urine under direct staff supervision was refused. Clean-catch urines collected and submitted by her mother showed large amounts of RBCs with reddish brown supernatant and pyuria (1+/high power field [HPF]). In contrast, the concurrently catheterized urine sample was normal without either hematuria or proteinuria. We sent her clean-catch urine for DNA STRs analysis, which revealed a mixed STRs profile containing body fluids or tissue from more than 1 individual (Fig 1).

The 13-year-old sister (Case 2) also had a long-standing history of seizures. On her first visit 3 years earlier, the hematuria was microscopic and not associated with proteinuria. Chemistry, serology tests and renal ultrasonography were within normal range. Because of the history of seizures, hematuria, and renal angiomyolipoma in her older sister, molecular genetic testing for tuberous sclerosis complex was done. The result was negative; however, her mother complained of gross hematuria with blood clots in the urine for 2 years. On review, clean-catch midstream urine samples collected during a routine follow-up visit to the outpatient clinic were grossly bloody with massive proteinuria (100 to >300 mg/dL). Serum concentrations of total protein, albumin, and IgG were normal. At our hospital, she underwent full investigations with nuclear renal scan, intravenous urography, kidney biopsy, CT, renal angiography, and cystoscopy. The only abnormality found was segmental attenuation of the glomerular basement membrane (151–241 nm). The pathologic changes were compatible with early/mild TBMD. However, the gross hematuria remained. Her mother claimed that the hematuria attacks occurred almost every day. Finally, she was admitted again for gross hematuria and acute gastritis. Clean-catch urine showed 100% normal RBC morphology. Before discharge, we inserted a straight catheter to collect her urine concurrently, which was normal without hematuria or proteinuria. The primary physician became concerned that she might be a victim of CAMS. A urinary catheter was then inserted and the balloon inflated with 5 mL of sterile saline. We clamped the Foley catheter, and it was released by a nurse every 2 hours for 1 day to observe the pattern of hematuria. All the urine was clear except for 2 episodes of gross hematuria in the drainage bag, with clean urine between the Foley catheter and drainage bag because the clamp was released by her mother (Fig 2A). In addition, the nurse reported that the balloon port of Foley catheter was stained red. We deflated the balloon immediately, and 10 mL of red-colored fluid was withdrawn. Analysis of the red-colored fluid revealed RBC 4+/HPF,
white blood cell 11–20/HPF, and proteinuria >300 mg/dL (Fig 2B). We sent the patient’s peripheral blood, the gross hematuria from the drainage, and the red-colored fluid evacuated from the balloon port for DNA STRs analysis. DNA from the child’s peripheral blood leukocytes showed a DNA profile from a single female (Fig 3A). However, the DNA STRs of the hematuria (Fig 3B) and aspirated red-fluid (not shown) from the balloon port of the Foley catheter revealed more than 2 peaks at every locus, and Y-chromosome STR typing indicated at least one male individual had contributed biological material to the samples. Table 1 delineates the different DNA STRs profiles among samples. Since then (5 months after identification of the sources of urinary blood and proteinuria), they have not come to our hospital for symptoms of hematuria or proteinuria.

DISCUSSION

Causes of hematuria are classified as either glomerular or nonglomerular in origin. A glomerular origin of hematuria is characterized by the presence of red cell casts, dysmorphic RBCs, small urinary RBCs, and significant proteinuria. In contrast, our cases showed a high percentage of normal RBC morphology in phase-contrast microscopy, and blood clots suggested a nonglomerular source of hematuria.

Angiomyolipoma is a well-known benign hamartoma involving the kidneys, liver, and other organs. It can occur sporadically or as part of tuberous sclerosis complex. Most small angiomyolipomas are asymptomatic and found incidentally on radiologic studies. Renal angiomyolipomas associated with lesions >4 cm in diameter and aneurysm formation are prone to spontaneous bleeding, which can lead to urgent nephrectomy. Epithelioid angiomyolipoma is a rare variant of angiomyolipoma, characterized by epithelioid cells that mimic renal cell carcinoma and have a malignant potential; therefore, long-term post-operative follow-up is mandatory. Case 1, who had a past history of epithelioid angiomyolipoma, had had partial nephrectomy. She presented to our department with gross hematuria and proteinuria. No evidence of recurrent or metastatic disease was found on the serial imaging studies; the normal, extensive investigations led to our suspicion of CAMS.
TBMD is characterized clinically by persistent or intermittent asymptomatic microscopic dysmorphic hematuria, minimal or no proteinuria, a uniformly thin glomerular basement membrane, and normal renal function. It has been reported that 34% (median; range 5%–65%) of children have episodes of macroscopic hematuria after exercise or concurrently with infections. In pediatric studies, proteinuria >500 mg/day is rarely seen in children with
In our Case 2, persistent asymptomatic gross hematuria had no association with upper respiratory illness. Her nephrotic range proteinuria and the presence of 100% normal red cell morphology suggested that TBMD was not the cause of her gross hematuria. In the absence of objective evidence of other causes of gross hematuria and with the observation of red-colored fluid with RBCs, white blood cells, and protein obtained from the Foley balloon, we suspected that her hematuria had been falsified or exaggerated.

Münchausen syndrome by proxy is a form of child abuse in which a caregiver, usually the mother, creates the appearance that their children are ill by fabrication, which can involve false or exaggerated history alone or, as in these children, contamination of laboratory samples. In some cases, the caretaker directly induces symptoms or illness in the child when the child is not really sick. Stirling used the term CAMS to extend the appellation of Münchausen syndrome by proxy to medical child abuse in which illness in a child is fabricated and/or induced by a parent, as well as that due to medical neglect, noncompliance, or even educational interference. In cases with small amounts of material or sample degradation, blood typing is impossible. STRs are short and repetitive sequences of DNA, usually 3 to 7 base pairs in length. The variation in the number of repeats at each STR location is what distinguishes one individual from another: STRs offer the advantage of short analysis time and produce highly discriminating results. Typically, as little as 1 ng of genomic DNA will yield a full STR profile to distinguish one DNA profile from another. In addition, STR also performs analysis on the Y sex chromosome, which is only found in males. Hence, STRs have been widely used in medical research such as paternity tests, identification of victims of disasters, and forensic science applications.

Blood type, minor blood group antigen in urine, and Y chromosome staining have been used for the diagnosis of CAMS. However, in our cases, the possible perpetrators (the mother and sisters) were all female with type O blood. Because of the poor power of discrimination of blood typing, a DNA STR test was chosen as a diagnostic tool in these patients. Verification of CAMS is difficult, with only 11.1% of the perpetrators admitting to their behavior. As with most previous reports, the mother denied having done anything to cause the children’s illnesses in these cases. Complex forms of CAMS, such as our cases, with previous or underlying renal abnormalities may require the use of a forensic test such as DNA STR analysis. In conclusion, in children with persistent gross hematuria, a diagnosis of CAMS or factitious hematuria should be considered after careful, complete, and repeated examinations of the hematuria.

<table>
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<th>Case</th>
<th>Clean-catch urine</th>
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Data are reported as genotypes. Ame, amelogenin; ND, nondetectable.
REFERENCES

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