Diagnosis and Management of Urolithiasis

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DR GARY N. FOX *(Associate Director, Family Practice Residency):* Urolithiasis is an important topic for family physicians. Between 2% and 5% of the population may be expected to pass a stone during their life span and about 20% of these require hospitalization.[1] Although statistics vary, about 40% of patients with an initial symptomatic stone will form another within 10 years.[2] Rather than concentrate on one patient, we will briefly review the courses of three patients seen in our practice who illustrate various aspects of the spectrum of stone disease. These patients are not completely typical, since two are older and two are female; the peak age of onset is between 20 and 30 years, and about 80% of patients are men. Our patients were all passing their first symptomatic stones.

CASE PRESENTATIONS

Case 1. Ms. A.N.

DR TUONG BUI *(Resident in Family Medicine)*: Ms. A.N., a 47-year-old woman, came to the emergency department because of 6 weeks of left flank and left abdominal pain. She described urinary frequency during exacerbations of the pain, but denied hematuria, dysuria, or a past history of similar symptoms. Mild left-sided abdominal and costovertebral angle tenderness were present on physical examination. The urinalysis showed 2 to 3 red blood cells and 4 to 5 white cells per high-power field. An intravenous pyelogram demonstrated a radiopaque calculus at the left ureterovesical junction. Urine culture grew greater than 10^5 *Escherichia coli* per milliliter. Serum calcium level was 2.82 mmol/L (upper limit normal [ULN], 2.50 mmol/L) (11.3 mg/dL, ULN 10.2 mg/dL). A repeat calcium determination was 2.70 mmol/L (10.8 mg/dL). Antibiotic therapy was initiated and urologic consultation obtained. On abdominal roentgenogram 4 days later, the calculus had passed, although it had not been retrieved in the urine strainer. Parathyroid hormone assay later returned significantly elevated, as anticipated with primary hyperparathyroidism.

Case 2. Mrs. D.C.

Mrs. D.C., a 28-year-old woman who drank two quarts of milk per day, was awakened by excruciating abdominal pain. She went to urinate and became nauseated, diaphoretic, and presyncopal with the pain. She passed a few drops of grossly bloody urine.

Three hours later, at the time of her examination, she had only a mild residual backache. Physical examination was normal except for mild bilateral lower quadrant and midline tenderness to direct palpation and moderate bilateral costovertebral angle tenderness. Urinalysis showed a large amount of blood with no leukocytes or nitrites. The patient declined an intravenous pyelogram (IVP). An abdominal film showed suspected phleboliths. Urine culture revealed no growth and serum multitest screening, including serum calcium, was likewise normal.

Mrs. D.C.'s gross hematuria cleared after 24 hours. She remained asymptomatic until 4 days later, when she experienced an episode of milder pain. She consented to an IVP, which revealed two small calcific densities partially obstructing the right ureter at the ureterovesical junction.

Over the course of the next several weeks, Mrs. D.C. experienced several episodes of mild discomfort responsive to acetaminophen. About 2 weeks later, she collected two crystals in her urine strainer that were found to be calcium phosphate on analysis. A 24-hour urine collection showed a calcium of 18.0 mmol/d (ULN, 5.0 mmol/d, 718 mg/24 h, ULN 200 mg/24 h). Over the next several months, serial serum calcium determinations continued to yield normal values; a repeat 24-hour urine collection confirmed the significantly elevated urinary calcium excretion.

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Case 3. Mr. E.B.

Mr. E.B, an otherwise healthy 68-year-old man, complained of 24 hours of moderate pain described as beginning in the right costovertebral angle area, radiating around the right flank, down into the superior portion of the right hemiscrotum. He had no urinary symptoms but had anorexia. The pain was unrelated to movement.

Physical examination was entirely normal. Urinalysis showed a specific gravity of 1.030 with moderate ketones and no blood. Acetaminophen proved to be adequate analgesia. The IVP was performed the next morning (after oral hydration) and demonstrated partial obstruction at the right ureterovesical junction with delayed function as a result of a radiolucent ureteral calculus. Urine culture and serum evaluations were normal.

By 24 hours after his first office visit, Mr. E.B. was asymptomatic and remained so through his course. Although he indicated he was straining his urine faithfully, no calculus was retrieved. Because of the difficulty visualizing his calculus, a repeat IVP was obtained after 3 weeks and was normal. Qualitative urine cystine screening was normal, and 24-hour urine tests are pending.

DIAGNOSIS OF URETERAL STONES

DR FOX: The topic of urolithiasis is complex. To keep this session focused, I would like to present a general overview of the diagnosis and nonsurgical management of acute ureteral stones and the metabolic evaluation of stone disease. Interventional methods of stone removal and specific therapeutic options for each potential metabolic disorder leading to urolithiasis is beyond the scope of today's discussion. We will start with the patient who has symptoms compatible with ureteral colic, proceed through the diagnosis, stone recovery, and metabolic studies. The goal of the investigation in the acute setting is to confirm the diagnosis and institute a plan that minimizes complications and maximizes outcome. The goal of the metabolic investigation is to identify any abnormality specifically enough so that appropriate preventive advice and medication (if necessary) can be given.

Ureteral colic is generally characteristic and presents little difficulty to the experienced clinician. Typically, the onset of the pain is abrupt, often severe, frequently beginning in the flank, varying in location as the stone migrates distally in the ureter, and often radiating to the testicles or labia. It is often accompanied by anorexia, nausea, or vomiting. The patient can often find no comfortable position, preferring movement to lying still, unlike patients with intraperitoneal processes. Blood pressure and pulse may be either increased or decreased from autonomic stimulation triggered by the stone. Examination of the abdomen is remarkable for the absence of signs of peritoneal irritation. Some abdominal or flank tenderness, however, is often present. Ileus of the intestine may occur. Pelvic and rectal examinations are generally normal, although testicular tenderness without palpable pathology may be present. In Mrs. D.C. and Mr. E.B., the presentations were sufficiently suggestive of stones to allow an accurate clinical diagnosis. With Ms. A.N., there was more clinical uncertainty prior to the IVP.

Additional historical features may lend support to the clinical impression, but neither does their absence exclude the diagnosis, nor does their presence confirm it. Remember that ureteral stone symptoms are a favorite of drug addicts seeking narcotics, so a past history of kidney stones may be willfully contrived for deceit (especially when allergy to contrast media coexists). Especially pertinent may be personal and family histories, history of vitamin D intake (increased calcium absorption) and vitamin C intake (increased oxalate production), and history of malignancy and metabolic or renal disease. In Mrs. D.C., her large intake of calcium may have contributed to her hypercalciuria.

If present, hematuria supports the diagnosis of urolithiasis, but one must remember several important caveats. Drug addicts can easily "arrange" a bloody urine. If drug seeking is in the differential diagnosis, a specimen voided during observation is important. Specimens obtained by catheterization may contain blood induced by the procedure. Also, hematuria is absent with the initial urine specimen in 15% to 30% percent of patients with stones,[3] contrary to many texts and even recent reviews,[1] as illustrated by our patient, Mr. E.B. Ms. A.N.'s hematuria was minimal, though present.

The IVP, the "gold standard" test, is generally recommended for patients with suspected urolithiasis. The major purposes of the IVP are to confirm the diagnosis, assess the degree of urinary tract obstruction, and identify anatomic abnormalities. The timing of the IVP depends on the clinical urgency. In a patient who is not severely ill, there is leeway in the timing of the IVP, as in Mr. E.B. and Mrs. D.C. If the IVP is not obtained at the time of the suspected ureteral colic, a roentgenogram of the kidneys, ureters, and bladder (KUB) should be considered. This study may provide supportive evidence for an opaque calculus that passes prior to an IVP and, with it, support for the diagnosis.[4] The IVP may be therapeutic as well as diagnostic; occasionally the dye will raise the intraureteral pressure sufficiently to drive the stone downstream.[1]

The IVP remains the initial imaging modality of choice because of unacceptably high rates of false-negative and false-positive tests when radionuclide studies and sonograms are used.[1,5] For patients unable to have a standard

IVP because of allergy to systemic administration of standard contrast dye, options for evaluation include IVP with use of the new low-osmolar contrast media and retrograde instillation of contrast media into the ureter under direct cystoscopic visualization. Abdominal computerized tomography without contrast enhancement has demonstrated acceptable sensitivity and specificity for all types of renal calculi, including the normally lucent uric acid stones.

MANAGEMENT OF UROLITHIASIS

Patients who have high-grade obstruction of a ureter generally have a clinical indication they are not doing well, specifically pain. A totally or almost totally obstructing stone can cause irreversible damage to a kidney within 1 to 4 weeks,[1,6] sooner if there is superimposed infection, and obviously requires close observation. Additionally, hospitalization may be required for the pain, suspected infection, dehydration, or preexisting urologic abnormality (particularly a stone affecting a single functioning kidney). Partial obstruction is often well tolerated by the patient and by the kidney, as illustrated in all our patients. Sonography may be useful for repeat evaluations in patients with partial obstruction, especially patients with altered sensation, such as patients with paraplegia or multiple sclerosis.

DR JOSEPH A. TRONCALE (*Director, Family Practice Residency)*: When complete or high-grade obstruction is present, do smooth muscle relaxants provide any clinical benefit?

DR FOX: A variety of medications that may promote smooth muscle relaxation, such as glucagon, nifedipine, and nitroglycerin, have been tried to decrease pain and promote stone passage. None has appeared effective. Narcotic analgesia remains the mainstay of acute therapy. If vomiting or intestinal ileus are present, the emetic and anticholinergic side effects of narcotic analgesics may exacerbate these features.

DR IVAN BUB *(Resident in Family Practice)*: Are there any guidelines about how likely a stone is to pass spontaneously?

DR FOX: Stones less than or equal to 4 mm diameter have greater than a 75% chance of spontaneous passage, whereas those greater than 8 mm have only a 10% chance.[1]

DR TRONCALE: How long can we wait for stones to pass and how do we follow them while waiting?

DR FOX: When the clinical situation (eg, absence of infection) allows conservative management, radiopaque stones may be followed with serial abdominal roentgenograms. Mrs. D.C.'s and Ms. A.N.'s stones were followed in this way, including documentation of passage. If the position of the stone remains stable for 6 months, spontaneous passage becomes less likely while incorporation of the stone into the ureteral wall becomes more likely.[6] These patients should be assessed for interventional removal. If the stone becomes difficult to visualize, but has not been retrieved, an IVP should be obtained for localization (or documentation of passage). While stones are being observed, all urine should be strained to capture the stone.

DR ELAINE KIRCHDOERFER *(Resident in Family Practice)*: Are there some generalities you can share about preventing recurrent stone formation?

DR FOX: Preventive therapy must be tailored to the underlying metabolic problem, which we will discuss next. Suffice it to say, at this point, that for the patient with a first calcium stone and no obvious metabolic disease identified with the recommended evaluation, several reasonable measures may be instituted. The patient should be withdrawn from medications and vitamins that may aggravate stone disease. A diet reasonable in protein, calcium, oxalate, and alkali should be advised. Liberal fluid intake should be encouraged, enough to produce 2 to 3 L of urine per day. Adequate fluid intake will maintain a dilute-appearing urine and cause nocturia once. When the patient arises to void at night, he should drink enough fluid so that the morning urine also appears dilute.

STONE TYPES AND METABOLIC DEFECTS

The urine of most normal individuals is supersaturated with respect to calcium oxalate, so, in principle, such stones can form in all persons. Factors that increase the level of supersaturation of stone-forming compounds, lower crystal-inhibiting substances, or decreased urinary volume increase the risk of stone formation. These factors may be intrinsic, such as dietary factors. Crystal formation begins by a process called nucleation. The nucleus of a crystal need not be the same substance as the crystal itself; uric acid or protein may be the nidus for calcium oxalate stones, for example.

First, I will review the metabolic studies for patients whose stones are retrieved and whose composition is determined, offering direction to the evaluation. There are four major types of stones. In order of frequency, these are calcium, mostly calcium oxalate; infection stones, also known as magnesium ammonium phosphate or struvite stones; uric acid stones; and cystine stones. Calcium stones are radiopaque; struvite and cystine, intermediate; and uric acid, radiolucent.

Now I have a question for you. Linus Pauling, Popeye, and patients with intestinal bypass operations are all at risk for calcium stones via a common mechanism. Can you name it?

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DR MICHAEL KIRK *(Resident in Family Practice)*: Hyperoxaluria.

DR FOX: Correct. A tricky, less-specific answer, alluded to previously, would be that all had increased levels of urinary saturation of stone-forming substances. Calcium stones, predominantly calcium oxalate, make up at least 80% of all recognized kidney stones. To keep life interesting, these stones also present the greatest range of possible metabolic causes. Hyperuricosuria may lead to a uric acid nucleus for calcium stones. Hyperoxaluria of any cause will increase the supersaturation of the urine with respect to calcium oxalate. Paradoxically, malabsorption syndromes, in which essential nutrients are not absorbed, can lead to exaggerated absorption of oxalate, a nonessential substance. Unabsorbed fat binds with calcium, freeing well-absorbed, unbound oxalate in the gut. Additionally, when bile salts are poorly reabsorbed in the distal small bowel, they stimulate oxalate absorption from the colon.[7] Additional causes of hyperoxaluria include a massive intake of oxalate-rich foods (chocolate, rhubarb, tea, spinach, beans), excess vitamin C intake (oxalate is a by-product of vitamin C metabolism), pyridoxine deficiency, an idiopathic category, and others. Hypocitraturia may also lead to calcium stone formation since citrate binds calcium, decreasing its availability for stone formation.[2]

Finally, hypercalciuria, itself of diverse origin, is the most commonly identified cause of calcium stones. Hypercalciuria is usually defined as 24-hour urine calcium in excess of 6.2 mmol/d (250 mg/24 h) for men and 5.0 mmol/d (200 mg/24 h) for women.[7] Hypercalciuria may be due to absorptive hypercalciuria (increased absorption of dietary calcium), renal hypercalciuria (faulty renal tubular reabsorption of calcium), hyperparathyroidism, renal tubular acidosis, vitamin D or drug ingestion, or excessive sodium intake (since calcium excretion parallels sodium excretion). Certainly hyperparathyroidism and renal tubular acidosis are important diagnoses to establish. In their absence, differentiating absorptive from renal hypercalciuria is usually not required.[7] The only subgroup of patients who form calcium stones in which women outnumber men is the group with hyperparathyroidism, in which about 65% of the patients are female.[8] Serum electrolytes are satisfactory for screening for renal tubular acidosis, which typically show a hyperchloremic, hypokalemic metabolic acidosis in this disorder.[1] Interestingly, Mrs. D.C.'s stones were calcium phosphate, which is associated with renal tubular acidosis, although her tests showed no evidence of this disorder.

DR KIRK: I thought struvite stones were also more common in women.

DR FOX: That is correct. In the various metabolic subgroups of those who form calcium stones, men significantly outnumber women except in the hyperparathyroid group. In fact, sex distribution is approximately equal in uric acid and cystine stones. The reason for the predominance of men with stone disease is that calcium stones are, by far, the most common stone type.

The laboratory studies that would be necessary to investigate the spectrum of metabolic possibilities leading to calcium stones are urinalysis, serum electrolytes, serum calcium, uric acid, creatinine, phosphorus, and albumin as well as a 24-hour urine collection for volume, pH, uric acid, calcium, oxalate, citrate, sodium, and creatinine (for adequacy of collection). Several serum calcium levels may be required to ensure episodic elevations are detected. Depending on the clinical situation and the abnormalities identified, further testing might be needed to define abnormalities, but such is beyond the scope of today's basic discussion. Note that the urine investigation takes place after the stone has passed.

When stones composed of substances other than calcium are identified, the investigation may be much more direct. Uric acid stones may form when there is massively increased uric acid excretion or when the urine is persistently acidic. Uric acid values above 4.16 mmol/d (0.70 g/24 h) for women and 4.76 mmol/d (0.80 g/24 h) for men in a 24-hour urine collection are considered elevated.[7] Hyperuricosuria may be due to uric acid overproduction or excessive dietary protein intake. The latter is most frequent in the elderly, as decreased urinary ammonia production is a common consequence of aging. Hyperuricosuria and hypercalciuria frequently coexist.

DR ELAINE KIRCHDOERFER: You mentioned hyperuricosuria as a cause for both calcium and uric acid stones. Is one more likely than the other to form in hyperuricosuric patients?

DR FOX: Hyperuricosuria leads to calcium stones four times more frequently than to uric acid stones; in fact, it is the second most common cause for calcium stones.

Infection stones form when urease-producing organisms, particularly *Proteus, Staphylococcus aureus,* and *Bacteroides,*[9] produce ammonia from urea, leading to magnesium ammonium phosphate crystals. Paraplegics, who have problems with neurogenic bladders and chronic infections, are the largest risk group for these stones. Cystine stones occur in patients with cystinuria. Either analyzing the stone or measuring the urine cystine content confirms the diagnosis. Cystine crystals are not seen in normal urine and are strongly suggestive of the cystinuria.[7] Interestingly, cystinuria can cause a false-positive nitroprusside test for ketones. You may recall that Mr. E.B. had a strongly positive dipstick for ketones. His qualitative urine for cystine was normal, and his ketone test became negative when his anorexia cleared.

Triamterene, usually prescribed in drug formulations containing triamterene plus hydrochlorothiazide, may cause urolithiasis. Although stones composed primarily of triamterene and its metabolites are rare, they do occur. An

increased frequency of kidney stones in patients with a personal or family history of stone formation who are exposed to triamterene has not been conclusively demonstrated. The data on triamterene stone formation are complicated by the concomitant use of hydrochlorothiazide. Because the thiazide drugs decrease the incidence of stone formation, an increase in stone formation caused by triamterene may be masked by the drug combination, producing no statistically apparent increase in frequency of stone formation. Approximately 0.4% of kidney stones contain some triamterene.[10,11]

When the stone is not recovered to assist in focusing the investigation, a comprehensive evaluation would include studies for all categories of stones. To the studies for calcium stones, a qualitative cystine screening examination and urine culture would be added. Some authorities recommend a detailed evaluation in all patients with stones, including those with first stones,[6] and those with a retrieved and analyzed stone. The rationale to pursue a more intensive evaluation is the evidence that many patients have more than one abnormality of urinary metabolite excretion[2] and the feeling that stone disease is more "malignant" than generally assumed.[6] The "do everything" view, however, is a minority one.

Recognizing that 50% to 60% of patients with a first stone will not form another stone during the ensuing 10 years, how extensive should the metabolic evaluation of a first stone be? Many of the simple, first-line evaluations may be unhelpful: history and physical examination may be nonspecific, stone analysis has a 70% chance of indicating calcium oxalate, and crystals of calcium oxalate and uric acid are normal in a urinalysis. A recent consensus conference panel recommended a "basic" evaluation for first stones, reserving additional testing for patients with multiple or recurrent stone disease.[2] Table 1 outlines the suggested initial evaluation. Abnormalities on these screening tests often mandate further testing, as, for example, the pursuit of Ms. A.N.'s hypercalcemia. If the screening test results are normal, some authors recommend repeating these examinations 1 year later, including the IVP, to further screen for metabolically active disease.[6] For children, patients at special risk, and those with recurrences, pursuing the 24-hour collections (and further testing based on identified abnormalities) is recommended.[2]

DR BUB: Our patients were all symptomatic for the first time from urolithiasis, but I remember you mentioned 24-hour urine results. Why were these obtained?

DR FOX: Mrs. D.C. had 24-hour urine testing for calcium because she is a woman in whom a calcium stone was demonstrated. The markedly elevated urinary calcium level was helpful in reinforcing the recommendation to reduce calcium intake, a recommendation at odds with what young women generally hear. As you recall, she had been drinking two quarts of milk per day. Mr. E.B. a 68-year-old with a radiolucent stone, might have a persistently acidic urine with hyperuricosuria. In discussing the options with the patient, he elected to have limited 24-hour urine testing done now. Ms. A.N., with her hypercalcemia, received no 24-hour urine testing.

TABLE 1. SUGGESTED INITIAL EVALUATION OF PATIENTS WITH A FIRST STONE

Clinical history
Physical examination
Stone analysis
Blood screening*
Calcium
Phosphorus
Uric acid
Creatinine
Electrolytes
Urine screening
Urinalysis
Urine culture if clinically indicated
Qualitative cystine if the stone composition is unknown
Intravenous pyelogram

**Multitest profile may be least expensive method of obtaining these measurements*

CONCLUSIONS

Urolithiasis is another clinical area where the knowledgeable family physician, with his knowledge of the patient, the patient's problems, temperament, and reliability, is ideally suited to negotiating the most appropriate timing and extent of the interventions and evaluation for each patient.

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