Renal Pelvocalyceal Abscess Secondary to Candida Albicans

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DR. RICHARD I. HADDY *(Assistant Professor, Department of Community Health and Family Medicine)*: At today's Grand Rounds we will discuss a case that we had on the inpatient service. We will start by having Dr. Bond present the case.

DR. JOHN A. BOND *(First-year Resident in Family Practice)*: This is a 63-year-old black woman who is a resident at one of our affiliated nursing care centers. She has a past history significant for hypertension, right-sided cerebrovascular accident, diabetes mellitus, and a left nephrectomy for a staghorn calculus in 1967. She presented to us with a two-day history of anuria and right upper quadrant pain. Her medications included 500 mg of chlorpropamide (Diabinese) taken orally daily, 25 mg of diphenhydramine (Benadryl) at bedtime, and for prophylactic purposes, sulfamethoxazole (Gantanol) taken as one 500-mg tablet twice a day. On initial examination she was an alert, black woman oriented to time, place, and person and in no acute distress. Her temperature was 101.2°F orally; pulse was 104 beats per minute; respiratory rate was 24 per minute and nonlabored, and her blood pressure was 170/100 mmHg. She had a firm, right upper quadrant abdominal mass that extended approximately 10 cm below the right costophrenic angle in the midclavicular line. On urinary catheterization no urine was obtained. Flushing the catheter produced only some urinary debris. Laboratory tests included a creatinine of 6.3 mg/dL and blood urea nitrogen (BUN) of 59 mg/dL. Her plasma glucose was 339 mg/dL.

A renal ultrasound showed a large cystic structure with a question of air-fluid levels near the kidney. A computed tomographic (CT) scan (Figure 1) showed it probably to be renal pelvis grossly dilated with an air-fluid level. A nephrostomy tube was implanted under fluoroscopy. Approximately 400 cc of gross pus was obtained. Gram stain revealed fungal hyphae and budding yeast, but no bacteria were seen at that time. The nephrostomy tube was left in place and irrigated, and the patient was treated with ampicillin and tobramycin, pending urine culture results. Dr. Shelton will show the x-ray films.

DR. JOHN A. SHELTON *(Third-year Resident in Family Practice)*: The radiologist was not sure whether the renal ultrasound examination showed this large cystic structure adjacent to the right kidney to be an extrarenal retroperitoneal mass, so we obtained the CT scan (Figure 1), which showed the mass filling up the right side of the abdomen. Additionally flat and upright films of the patient's abdomen showed all of her bowel gas to be on the left side of the abdomen. It turned out that the enlarged renal pelvis had pushed everything in the abdomen over to the left side, which was confirmed by the CT scan. There was also an air-fluid level that led to concern about infection.

DR. BOND: The nephrostogram (Figure 2) shows a grossly dilated renal pelvis as well as a dilated ureter with what appears to be a distal filling defect.

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viously with ketoconazole in the nursing home?

DR. C. MICHAEL DAY *(Third-year Resident in Family Practice)*: Yes. Her nursing home course was significant for recurrent dysuria, frequency, and recurrent Candida vaginitis with obvious irritation. Her condition was treated as a Candida vaginitis many times, and it always recurred within a week or less. Her dysuria would also always come back. Her several urine cultures almost always showed yeast. She was finally started on ketoconazole in the nursing home, which provided some subjective relief for maybe less than a week, but her symptoms resumed at the end of the week. She was a diabetic, and I thought that better control of her glucose levels might help. That was when we started the oral hypoglycemic agent.

DR. BOND: While she was in the hospital, her blood glucose was regulated with insulin: 20 units of NPH and 5 units of regular insulin each day.

DR. HADDY: Dr. Curry, do you have any comments?

DR. R. WHITNEY CURRY, JR. *(Associate Professor, Department of Community Health and Family Medicine)*: We never really established the cause of her ureteral obstruction. It was clear when she came in that her ureter was obstructed, but whether it was a stone or a necrotic papilla or fungal debris was not determined, and we do not know that she will not have this problem again; the nephrostomy tube has been clamped for 48 hours and she is still urinating normally.

DR. HADDY: Were any fungus balls noted? Sometimes that will do it. They are large enough to visualize, and they often look like kidney stones.[1]

DR. BOND: No, none was noted.

DR. ROBERT A. JAMES *(Second-year Resident in Family Practice)*: Why was ketoconazole chosen for an apparently severe Candida urinary tract infection?

DR. SHELTON: Basically she was never very sick. She just wasn't passing urine and her creatinine was high. We discussed her treatment with our consultant, and he felt that he didn't want to give her a potentially toxic drug. She didn't have evidence of a systemic Candida infection.

DR. HADDY: Dr. Petry, would you comment on some of the past history and social aspects of the case?

DR. L. JEANNINE PETRY *(Assistant Professor, Department of Community Health and Family Medicine)*: Mrs. Murphy was born in 1921. She had had kidney and bladder infections since her teenage years, which culminated at the age of 46 years when she had a left nephrectomy for renal stone disease and recurrent infection.

She has had hypertension, and at the age of 51 years she had a right-sided cerebrovascular accident with resultant left-sided paralysis. She went to live with her youngest son. To get around in the house, she would push herself in a chair on the wooden floors. She stayed with her son until 1977, when at the age 56 years she went into a nursing home because, she said, she was "too much trouble" and wanted to alleviate pressures on her son.

In the nursing home, glucose intolerance was diagnosed and controlled with diet. In 1983, at the age of 62 years, she was noted to be lethargic and nauseated for two days. She was hospitalized and noted to have vaginitis and a urinary tract infection. Over the next three days she developed azotemia, and she was sent to another hospital to the care of a urologist, where she had a urine culture that showed yeast. An intravenous pyelogram and a retrograde pyelogram showed hydronephrosis, pancalyceal dilatation, and an obstructive right ureteropelvic junction stricture of the remaining right kidney. A nephrostomy tube was placed by CT-guided methods, and then a stint was placed from the right kidney pelvis to the bladder. With this stint, urinary drainage returned and her renal function returned to normal. She was returned to a nursing home, where she was placed on sulfamethoxazole for bacterial suppression.

In January 1984 she was rehospitalized to have the stint removed. An intravenous pyelogram and retrograde pyelogram were done after the stint was removed. There was some fixed dilatation of the ureteropelvic junction, right hydronephrosis, and a suggestion that the renal pelvis was enlarging. The urologist advised surgical repair of the ureteropelvic junction, but she declined. The urologist's recommendation was that if she went back into renal failure to strongly consider attempts at surgical repair of her right ureteropelvic junction. She then went to our affiliated nursing home to the care of our family practice residency program.

At the nursing home she was described as being

a cooperative and very positive person. She participated in the activities of the nursing home and spent most of her waking hours in a wheelchair, wheeling herself around.

As far as her functional assessment is concerned, her general cognitive, emotional, behavioral, and social interaction skills were unimpaired. She was not incontinent, even though she often had urinary frequency because of her recurrent urinary tract infections. She had some fixed limitation in walking and had been in physical therapy at the nursing home to improve her gait.

She remained on prophylactic sulfamethoxazole at the nursing home. In May 1984 she had a urinalysis that showed gram-negative rods and yeast and was given ampicillin. She also had vaginitis that on potassium hydroxide (KOH) smear was positive for yeast, and was given miconazole cream. Until her present episode of anuria she has had four different urine cultures positive for yeast. After the third positive culture she was given a ten-day course of ketoconazole. It was approximately one month later when she developed the anuria, which led to her current hospitalization.

Finding out about past hospitalizations, the previous ureteropelvic junction stricture, the surgical intervention with a stint, and the recommendation that she have surgery on this ureteropelvic junction helps us put together what is going on with her right now. It is interesting to theorize how long she may have been cultivating Candida in her renal pelvis. What we are seeing now is certainly not a sudden problem.

At the nursing home she was extremely functional. One of the goals during hospitalization was to make sure that she has physical therapy to help return her to the functional status she had in the nursing home. Older patients with acute illnesses requiring hospitalization often lose some of their functional status, and many of them never regain the same level of function. If they do, it can take a number of months. Dr. Jernigan, do you have any comments on functional status and the effects hospitalization can have on nursing home patients?

DR. JAMES A. JERNIGAN *(Associate Professor, Department of Community Health and Family Medicine)*: Very little research has been done on this subject because demographic information has just begun to trickle in on the frequency of hospitalizations of nursing home patients. With the decline of homeostatic reserve, as you mentioned, there certainly is a major problem in the aging process. This individual has diabetes, which hastens the pathophysiological process of aging, and she has a number of problems in addition to her age. It is generally most remarkable when someone who has an acute problem like this returns to the functional status they had before the hospitalization.

DR. HADDY: This represents an interesting and unusual presentation of a Candida albicans urinary tract infection. A few words are in order about Candida albicans and the drugs that have been used in treating this patient.

Candida has been grouped with the fungi imperfecti, since no sexual stage has been identified. They reproduce by budding, and are identified by seeing hyphae and pseudohyphae on KOH smears. A rapid, presumptive test can be done by putting the organism in serum and observing germ tube formation, which are small surface projections on the cell. There are also more specific metabolic tests that can be done to confirm identification of the organism. Candida albicans is a frequent colonizer in man and in animals.[2]

What kinds of immune processes does man have to fight Candida? Candida isn't really a common skin colonizer, but any time that the skin or mucous membranes are disrupted, the site is susceptible to Candida invasion. It is thought that the body needs intact T-cell function for resistance to chronic mucocutaneous candidiasis. However, once the organism is in the blood, the polymorphonuclear leukocytes are the main defense. They phagocytize the blastospores and are able to damage the pseudohyphae. Diabetes, of course, predisposes to Candida infections, classically cutaneous, not disseminated, candidiasis. Antibiotics suppress bacterial flora and allow overgrowth. Polyethylene catheters and prosthetic materials also serve as hosts for Candida infection. General immune suppression, cancers, hyperalimentation fluid, multiple abdominal gastrointestinal surgeries, and use of steroids all predispose to Candida infection.

Candida albicans is responsible for a wide variety of clinical manifestations. These include many

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gastrointestinal syndromes including thrush, Candida esophagitis, and gastrointestinal candidiasis, vaginitis, and cutaneous candidiasis syndromes such as folliculitis, balanitis, onychomycosis, diaper rash, and chronic mucocutaneous candidiasis. Central nervous system candidiasis and pulmonary candidiasis are occasionally seen in debilitated patients. Candida can cause mild carditis, endocarditis, and pericarditis, usually in debilitated patients, as well as arthritis, osteomyelitis, and peritonitis. Particularly in patients on dialysis, disseminated candidiasis and candidemia may occur. Again, these latter syndromes are usually in very ill and debilitated patients. That brings us to urinary tract candidiasis.

Urethral candidiasis can occur in both men and women. In men, it is thought to be caused by sexual contact with a women who has Candida vaginitis. Urethritis in a women is thought to be caused by the Candida vaginitis itself. Candida cystitis is most often associated with an indwelling catheter. In the absence of bladder instrumentation, cystitis is most often associated with diabetes.

As family physicians, you will occasionally be called by a nursing home and be told that a patient's urine culture is positive for Candida. Or, you might be called by a hospital and told a patient's blood culture is positive for Candida.

The first thing to do is always to look for an indwelling catheter or intravenous tube of some sort. In the case of candiduria, if the patient does not need the catheter, remove it. Often, changing the catheter will also solve the problem. In the case of a patient on intravenous hyperalimentation, if a positive blood culture for Candida is obtained, you can often solve the problem by removing or changing the intravenous catheter. However, never completely relax because at that point the patient is not necessarily cured. Always be sure to follow the patient, repeat the cultures, and make sure the patient is not febrile or showing continued signs of infection before dismissing the problem. If the patient shows continued signs of infection, consider further treatment with some of the antifungal agents to be discussed later.

There are thought to be two kinds of urinary tract involvement: primary and secondary. Primary involvement means originating from the ascending route. Papillary necrosis, calyceal invasion, fungus ball formation, and perinephric abscess have been described. The case that we presented today of a pelvocalyceal abscess or a renal pelvic abscess is rare. I could find only one or two cases in the literature.[1] Secondary infection refers to spread of infection to the kidney hematogenously from another source.

In this patient a positive culture for Candida taken directly from pus obtained from the renal pelvis constitutes good evidence of an abscess caused by Candida. We have no evidence of hematogenous spread, since we have no positive blood cultures. Her diabetes, underlying renal disease, Candida vaginitis, and chronic use of antibiotics were probably all contributing factors to her chronic candiduria and eventual abscess.

Some discussion about ketoconazole[3,4] is relevant at this point, since this is a drug that is assuming an increasingly important role in clinical medicine. Ketoconazole is a broad-spectrum imidazole compound, similar to clotrimazole, which we would use, for example, intravaginally. However, unlike clotrimazole ketoconazole can be absorbed through the gastrointestinal tract. The mechanism of action is that it is fungistatic. It inhibits the 14-demethylation of lanosterol, the precursor of ergosterol, which is necessary for integrity of the fungal cell membrane. Thus, ketoconazole interferes with the synthesis of ergosterol. As for the pharmacology, it is well absorbed orally and reaches a peak serum concentration of 2 to 5 mg/mL about two or three hours after administration of a single 200-mg tablet. Ninety-nine percent protein bound, mainly to albumin, it is primarily metabolized in the liver to an inactive metabolite that is excreted in the bile. Alterations in the dosage are not usually required in patients with kidney disease, since only 13 percent of the active drug is excreted into the urine. As far as efficacy, ketoconazole appears to be effective against paracoccidioidomycosis (for which it may be the drug of choice), histoplasmosis, coccidioidomycosis, and chromomycosis, but does not appear to be effective against sporotrichosis, mycetomas, or aspergillosis. Although it is very effective against chronic mucocutaneous candidiasis, and is very good, interestingly enough, against Candida sepsis, it is less effective against

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Candida urinary tract infections, probably because it is poorly excreted in the urine. Even though ketoconazole is less toxic to the host than are most available drugs for fungi, it causes nausea in about 3 percent of the patients and gynecomastia in some patients because it inhibits testosterone synthesis. It also causes some liver toxicity. Elevations of the liver enzymes, for example, or cases of massive hepatic necrosis, coma, and death have been reported in the literature.

There is good reason to try ketoconazole on this patient. If most of the abscess were drained surgically, one could assume that the patient had been mostly cured in this way. The low toxicity of ketoconazole in an elderly patient who has already some renal impairment makes the drug good adjunctive therapy.

Explanation is in order as to why amphotericin B is being tried now,[5] after the ketoconazole. Amphotericin B is active against most fungi that can cause deep-seated infections and is probably still the mainstay of therapy, surpassing flucytosine against severe fungal disease. The mechanism of action is that it disrupts the integrity of the cellular membrane of susceptible yeast and fungi. Sites of bonding are the sterol moieties of the cell membrane of the fungi. It is active against Histoplasma capsulatum, Blastomyces dermatitidis, Coccidioides immitis, Cryptococcus neoformans, Candida albicans, and other Candida species as well as Torulopsis glabrata, Aspergillus fumigatus, sporotricosis, and Mucor species. So unlike flucytosine, amphotericin B is a broad-spectrum drug, as is ketoconazole.

Usually a test dose of 1 mg is given over two to three hours to determine whether the patient tolerates it. Then daily dose increments of 5 mg are added until about 0.6 mg/kg is achieved. One has to get a creatinine reading every other day because amphotericin B is an extremely nephrotoxic drug. Azotemia will develop in most patients. The total dose for most courses of this drug against most fungi is about 2 to 4 g.

Adverse effects include nephrotoxicity, which develops within two weeks. A creatinine level of up to about 2 mg/dL is acceptable. If the level goes above that, it is necessary to stop giving the drug for a while and wait until the creatinine level comes down. Side effects include headache, nausea, vomiting, and fever. One can reduce some of these side effects by premedicating with diphenhydramine (Benadryl) or aspirin, or by adding 25 mg of hydrocortisone succinate in the intravenous bottle. One also sees hypokalemia, hypomagnesemia, anemia, and thrombophlebitis at the intravenous site.

The first reason amphotericin B was used is that the urine culture continued to be positive for Candida while the patient was on ketoconazole; in other words, ketoconazole failed to control the Candida infection. The second reason was the potential severity of the disease. If the patient had not been treated, the same infection would be more likely to recur. Amphotericin B is prescribed in low dosage and is administered very cautiously because of the patient's overall limited renal capacity.

DR. KRAVITZ: That ketoconazole is not renally excreted would seem to be a problem in this patient.

DR. HADDY: This patient has severely impaired renal function in that her one remaining kidney is working poorly. Ketoconazole is not a nephrotoxic drug and seemed worth a try. Antifungal agents are very interesting. We know, for example, that amphotericin B does not get into the cerebrospinal fluid well by the intravenous route, yet cases of cryptococcal meningitis have been cured with amphotericin B.

DR. JERNIGAN: You may want to give some thought to her immunocompetence—her cell-mediated disease and cytosensitivity. I would imagine she is anergic. But, if she's not, the prognosis would be better. If she is, there may be various contributing factors, such as lack of protein, zinc, and so on.

DR. KRAVITZ: I recently had a patient with urinary candidiasis who was frustrating to treat. It becomes difficult to tell when Candida is a colonizer and when it is pathologic. This case certainly highlights the fact that candidiasis can be pathologic, whereas usually it is ignored. How does one decide when this is an infection that needs to be treated?

DR. HADDY: The phenomenon of candiduria is becoming increasingly common, and I agree it can be very serious. A blood or urine culture positive for Candida is indeed often ignored. I suggest that it be considered pathologic until it is proved

not to be. What you do would depend on a combination of the clinical course and the laboratory studies that can be done. For example, if a patient is not having symptoms of cystitis and is not febrile, then I would worry less about it. However, she might still be a good candidate for ketoconazole if her cultures continue to be positive and if she's in relatively good health. If you can eradicate the organism with minimal toxicity, it might make both you and the patient feel better.

DR. PETRY: With a fixed obstruction somewhere between the renal pelvis and the bladder, we can drain her Candida abscess, give her antifungal medication, and suspect that she is going to get into trouble again. She already has been recommended in the past to have ureteral revision. Planning for adequate functional and nutritional status is therefore important. If we are going to take this patient to surgery later, we will want to pay attention to both of those areas before and after surgery.

DR. CURRY: The problem now, though, is that she really does not have a stenotic lesion. In fact, her ureter is dilated and the radiologist has told us that it has normal peristalsis. At this point, we don't have anything to operate on.

DR. HADDY: That is a good point. We will see what develops. Thank you all for your participation.

References

1. Tennant FS Jr, Remmers AR Jr, Perry JE: Primary renal candidiasis: Associated perinephric abscess and passage of fungus balls in the urine. Arch Intern Med 1968; 122:435-440
2. Edwards JE Jr: Candida species. In Mandell GL, Douglas RG, Bennet JE (eds): Principles and Practice of Infectious Diseases. New York, John Wiley & Sons, 1985, pp 1435-1447
3. Smith EB, Henry JC: Ketoconazole: An orally effective antifungal agent: Mechanism of action, pharmacology, clinical efficacy and adverse effects. Pharmacotherapy 1984; 4(4):199-204
4. Deutsch PH, Quintilliani R: Ketoconazole. Conn Med 1984; 4(4):216-221
5. Hermans DE: Antifungal agents used for deep-seated mycotic infections. Mayo Clin Proc 1977; 52:687-693