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Original Articles

FUNGAL BEZOARS OF THE UPPER URINARY TRACT

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ABSTRACT

We report our experience with 6 cases of upper tract fungal bezoars involving 9 renal units—3 bilateral aspergillomas and 3 Candida bezoars. The Aspergillus bezoars were notably more morbid: 2 patients required nephrectomy after failure of medical therapy, whereas the 3 unilateral Candida bezoars all resolved with medical therapy and endourological access. In 1 patient whose aspergilloma was resistant to amphotericin B the investigational drug itraconazole proved effective. These opportunistic infections, seen increasingly in immunocompromised patients, can present a difficult management problem. A combined approach is necessary, including medical therapy with topical and systemic antifungal agents, and endourological access for extraction, lavage and debulking. (*J. Urol., 143: 447–451, 1990*)

Fungal infections of the upper urinary tract are relatively uncommon and fungal bezoar formation is a particularly unusual complication. However, reports of systemic fungal infections have increased in recent years.[1,2] These opportunistic infections invariably present as a complication of impaired host resistance and, thus, urologists may be expected to encounter them ever more frequently. In the setting of an obstructive uropathic condition secondary to an upper tract bezoar the sequelae in an immunocompromised patient can be devastating. Such patients often are in fragile if not critical condition and eradication of the offending organism can prove to be a protracted, complicated course requiring combined medical and surgical intervention. We review our experience with 6 patients with fungal bezoars of the upper urinary tract involving 9 renal units (the largest series reported to date), and present a medical and surgical approach to the management of these challenging cases.

PATIENTS AND METHODS

We identified 6 patients as having been treated for fungal bezoars of the upper urinary tract from 1980 to 1988. The medical records were reviewed and the important clinical characteristics were analyzed. Patient 4 has been reported on previously.[3]

RESULTS

All patients were men 28 to 62 years old (mean age 43 years). With 1 exception, the chief complaint at presentation was flank pain. Patient 3 presented with passage of fungal debris per urethram. Only 1 of the 3 patients with Aspergillus presented with fever and chills, which were absent in all 3 Candida patients. No patient in this series presented with leukocytosis or azotemia. However, all patients had pyuria and microscopic or gross hematuria. No patient had positive blood cultures for fungus either at presentation or during the extensive hospitalizations. No extra-urothelial involvement was demonstrated in any patient.

Diagnosis. Hydronephrosis was documented in 2 patients with ultrasonography and subsequent pyelography demonstrated obstruction. In the other 4 patients, excretory urography (IVP) was the initial study documenting upper tract obstruction. The diagnosis of funguria was established with passage of fungal debris per urethram (2 patients), aspiration of ureteral washings (3) and nephrostomy tube drainage (1). The interval from initial presentation to diagnosis ranged from 4 to 13 days in 4 of the 6 patients, while 1 had experienced symptoms for 5 months before diagnosis and 1 had had intermittent flank pain for 2 years.

Risk factors. All patients had diabetes mellitus (5 were insulin-dependent). The mean serum glucose level at presentation was 389 mg./dl. Three patients had a history of intravenous drug abuse. Patient 3 also had been on long-term intravenous antibiotics for chronic osteomyelitis. No patient reported a classical environmental exposure to Aspergillus (that is construction sites, aviaries and so forth). However, Aspergillus has been associated with marijuana[4] and it is reasonable to assume that our 2 Aspergillus patients with a history of intravenous drug abuse were exposed to marijuana.

Organism. Two patients were infected with C. albicans, 1 with C. tropicalis, 2 with A. flavum and 1 with Aspergillus species unspecified. The 3 patients with Aspergillus had bilateral involvement. Therefore, 9 renal units with fungal bezoars were reviewed.

Length of hospitalization. Prolonged hospitalization was related either to a delay in diagnosis (patient 5) or to the lengthy treatment course of intravenous and topical amphotericin B. The 3 patients with aspergillosis required an average of 5 months of hospitalization. In contrast, the 2 patients with candidiasis who required prolonged intravenous and topical antifungal medication had an average inpatient course of 6 weeks.

Therapy (see table). In patient 1 the Candida bezoar resolved with topical irrigation and intravenous amphotericin B, and urine cultures were negative. He left the hospital against medical advice and has been lost to followup. In patient 3 the Candida bezoar persisted despite topical, intravenous and oral antifungal therapy, and required percutaneous nephroscopy, lavage and extraction. This was followed by resumption of the medical therapy and complete resolution of the lesion. Patient 2 underwent balloon dilation of a presumed ureteropelvic junction inflammatory stricture and irrigation via ureteroscopy of

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a small obstructing Candida bezoar. He refused any adjunctive medical therapy and was lost to followup until 5 months later when symptoms relapsed. At that time a percutaneous nephrostomy tube was placed. Extraction and lavage of the bezoar were followed by antegrade endoscopic pyelotomy to treat the stricture.

The protracted course of patient 5 reflects the multiple medical complications (see table) and a delay in diagnosis. For 5 months he had multiple hospitalizations for flank pain of unclear origin but post-traumatic stress disorder was diagnosed mistakenly and he was treated with antidepressants. After the fungal bezoar was diagnosed retrograde irrigation via a ureteral stent was sufficient to clear the left upper tract Aspergillus. The right side was cleared only after ureteroscopic direct debulking and irrigation of debris followed by further retrograde irrigation with amphotericin B. Patient 4 had early aggressive surgical debulking of the right pelvic aspergilloma via an open pyelotomy. He received intravenous amphotericin B for 6 weeks but without concurrent topical irrigation and he eventually required right nephrectomy for a persistent urocutaneous fistula with complete ureteropelvic junction obstruction. The renal pelvis and proximal ureter were almost entirely occluded by fibrous reaction, with complete sloughing of the renal papillae and replacement with necrotic debris, branching hyphae and granulation tissue. The renal cortex generally was uninvolved, thus, demonstrating the presumed ascending route of infection.[3] However, the left collecting system, which had a swollen fungal volume, cleared with intravenous amphotericin B. Patient 6 presented with cachexia and right flank pain. An IVP revealed multiple filling defects in the right renal pelvis believed to represent a malignant process. Attempts to obtain specimens for cytological testing eventually revealed a complete inflammatory stricture at the ureteropelvic junction. Urine samples from the right renal pelvis could not be collected by either ureteral catheterization or ureteroscopy. Subsequently, a right nephrostomy tube was placed and Aspergillus eventually was cultured. A nephrostogram revealed numerous filling defects (fig. 1). The patient underwent debulking of the bezoar via rigid nephroscopy with dramatic resolution radiographically, and he was treated with topical irrigational and intravenous amphotericin B. However, the disease relapsed and progressed, and he required nephrectomy. Gross inspection demonstrated tenacious bezoar material filling the collecting system with apparent parenchymal sparing (fig. 2). Histopathological examination confirmed Aspergillus hyphae limited to the collecting system (fig. 3). Just before nephrectomy, contralateral involvement was first demonstrated in the left upper pole and subsequent in vitro sensitivity testing showed this fungus to be relatively resistant to amphotericin B. The investigational drug, itraconazole, was begun in addition to retrograde irrigation with amphotericin B. After 4 weeks the defect resolved and the urine became free of fungus. At 3 months urine cultures were

Results of treatment in 6 men with Candida or Aspergillus bezoars

Pt. —Age No.	Risk Factor	Treatment		Duration of Hospitalization	Complications	Outcome
		Medical	Endourological/Surgical			
			Candida			
1—36	Insulin-dependent diabetes mellitus	Intravenous amphotericin B	Retrograde ureteral catheter, amphotericin B irrigation	4 wks.	None, lost to followup	Neg. urine
2—62	Noninsulin-dependent diabetes mellitus	—	Ureteroscopy, irrigation and lavage, dilation of ureteropelvic junction stricture	2 days	Recurrent stricture and bezoar at 5 mos.	Filling defects cleared
		Sodium bicarbonate, 5-flucytosine	Endopyelotomy	3 days	None	Filling defects cleared, neg. urine
3—28	Insulin-dependent diabetes mellitus, intravenous drug abuse, antibiotics	Intravenous amphotericin B	Percutaneous nephrostomies of upper and lower pole, failed retrograde Double-J* ureteral stent, antegrade Double-J ureteral stent, amphotericin B irrigation, nephroscopy, lavage and extraction of bezoar, continued amphotericin B irrigation	2 mos.	None	Filling defects cleared, neg. urine
			Aspergillus			
4—46	Insulin-dependent diabetes mellitus, intravenous drug abuse	Sodium bicarbonate, 5-flucytosine, intravenous amphotericin B	Rt. renal exploration, pyelotomy, removal of bezoar, lt. retrograde ureteral catheter, amphotericin B irrigation, rt. nephrectomy	4 mos.	Urocutaneous fistula, recurrent rt. bezoar	Rt. nephrectomy, filling defects cleared, neg. urine
5—35	Insulin-dependent diabetes mellitus	Intravenous amphotericin B, rifampin	Bilat. retrograde ureteral catheters, amphotericin B irrigation, rt. ureteroscopic lavage	6 mos.	Sepsis, endocarditis, congestive heart failure, acute renal failure, anemia	Filling defects cleared, lost to followup
6—50	Insulin-dependent diabetes mellitus, intravenous drug abuse	Intravenous amphotericin B, rifampin, itraconazole	Failed rt. retrograde Double-J stent, ureteroscopy, rt. percutaneous nephrostomy, lavage, extraction of bezoar, amphotericin B irrigation per lt. nephrostomy, then per ureteral catheter, rt. nephrectomy	6 mos.	Recurrent rt. bezoar, resistance to amphotericin B, amphotericin B renal toxicity, adrenal insufficiency	Rt. nephrectomy, filling defects cleared, neg. urine

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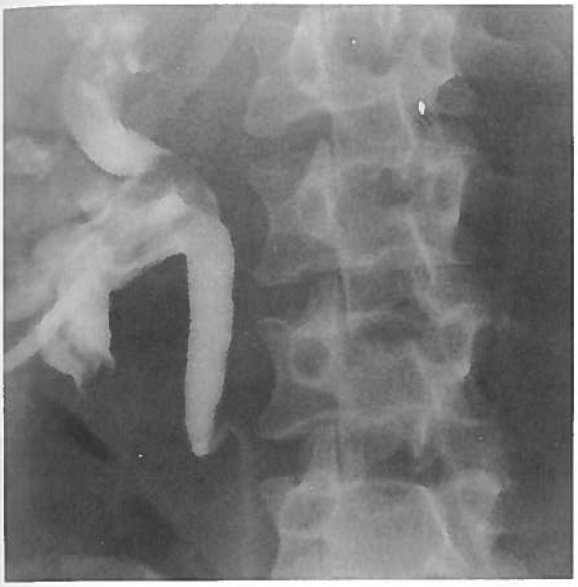

FIG. 1. Nephrostogram with Aspergillus bezoar

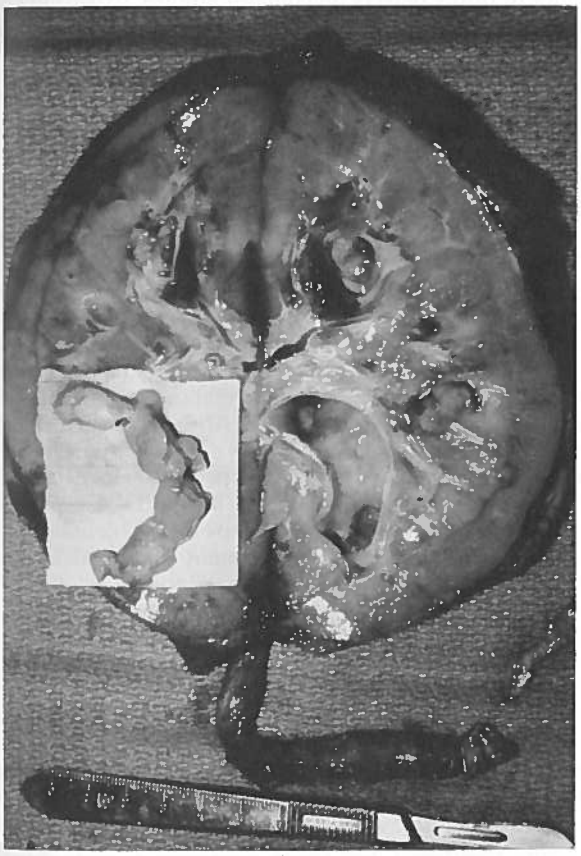

FIG. 2. Gross specimen of kidney with aspergilloma in collecting system. Renal parenchyma appears to be spared.

negative and the patient had no recurrent filling defects. He remains on itraconazole (200 mg. orally 2 times daily), which will be continued for 1 year. To date the drug has produced no adverse effects.

DISCUSSION

During the last 2 decades the reported incidence of invasive fungal infections has increased.[1,2] Although fungi are normal flora that rarely are pathogenic in the healthy human host, they can have life-threatening sequelae in chronically ill and

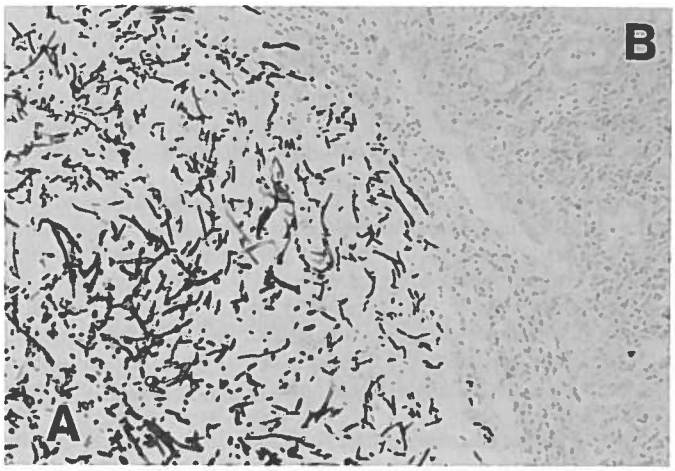

FIG. 3. Aspergillus mycelium limited to collecting system. *A*, Aspergillus in collecting system. *B*, spared renal parenchyma. H & E, with silver stain.

debilitated patients. The most common predisposing factor for fungal urinary tract infection is diabetes mellitus. Other associated conditions are prolonged antibiotic therapy, steroids, immunosuppressive therapy in allograft recipients and cancer patients (who also may be receiving chemotherapy or radiation), collagen vascular disease, intravenous drug abuse, congenital or acquired urinary tract obstruction, neonatal prematurity, indwelling catheters, stones and foreign bodies.[5] Interestingly, however, fungal bezoars have not been reported to date in patients with the acquired immunodeficiency syndrome.

Only approximately 50 cases of fungal bezoars of the urinary tract have been reported in the literature. The great majority have been associated with Candida species,[6] with 4 reports of Torulopsis.[7-9] There have been 13 cases of Aspergillus bezoars,[3,10-12] and 1 each of Penicillium[13] and Mucormycosis.[14] These are the only organisms known to produce a bezoar, the tenacious conglomeration of fungus and necrotic debris formed around an interwoven network of hyphae. Papillary necrosis secondary to parenchymal fungal infection or diabetes contributes sloughed tissue to the bezoar mass. Stones or suture material also may form a nidus for bezoar propagation.[10,15] Torulopsis bezoars are somewhat different from the others, since Torulopsis lacks hyphae but forms an organized obstructive coagulum in the upper tracts.[16] This is more flocculent and less tenacious, and, therefore, may be easier to disrupt and debride. Torulopsis is related closely to Candida and also is considered by some as a Candida species, C. glabrata.[17]

Beilke and Kirmani reported 3 cases of candidal pyelonephritis associated with obstructing bezoars and no other organ involvement.[9] Two cases were managed successfully with percutaneous or ureteral stent irrigation and systemic antifungal therapy; the third, who had had systemic amphotericin B therapy, died of pancreatic cancer. No local irrigation was performed. Fisher and associates reported 5 cases of Candida bezoars requiring transplant nephrectomy in the 2 transplant recipients, while the other 3 were managed successfully with either systemic therapy alone or systemic and irrigational antifungals.[6] Other recent cases of candidal bezoars of the upper tract have been managed successfully with endourological access and local irrigation with systemic antifungal medication.[18,19]

Bezoars of the upper urinary tracts can occur secondary to either ascending funguria or hematogenous dissemination with renal parenchymal involvement. Systemic candidiasis involves the kidney in more than 85% of the cases versus 12% with renal involvement in disseminated aspergillosis.[20,21] In the absence of systemic involvement, ascending infection is considered to be the most likely source. As in our series, it appears

that the urothelium serves as an immunological barrier to progression of disease with parenchymal invasion. The immunological mechanism by which infection remains confined to the collecting system remains to be elucidated. This phenomenon is demonstrated in figure 2, where a clear demarcation is seen between the fungal bezoar and the spared renal parenchyma.

Diagnosis of an upper tract fungal bezoar is confirmed with urine cultures localizing the site of infection. All of our patients had localizing cultures by either a percutaneous nephrostomy tube or transurethral ureteral catheters. Filling defects of the upper urinary tract can represent other entities, including tumor, blood clots, papillary necrosis or calculi. Multiple large volume urine cultures may be necessary to identify Aspergillus, since a single negative culture is insufficient evidence of fungal sterility.[3]

Fungal infections are among the most difficult to cure, principally owing to a paucity of effective antifungal medications. Fungi thrive at acid pH and alkalization of the urine is a helpful adjunct to medical therapy. Sodium bicarbonate may be administered either by the oral or irrigational route.[22] 5-Flucytosine is an oral agent that interferes with fungal ribonucleic acid synthesis, with high activity against Candida and only moderate activity against Aspergillus. It is excreted mainly in the urine, is synergistic with amphotericin B and, therefore, frequently is given concurrently. Resistant fungal strains develop in up to two-thirds of the patients who receive 5-flucytosine, and reversible liver toxicity and bone marrow suppression are the major adverse effects.[2]

Amphotericin B binds to cell membrane sterols and causes fungal cell lysis. It is indicated for systemic disease and is excreted poorly in the urine.[5] The major toxicity of this drug is renal dysfunction in up to 80% of the cases but it generally is reversible if the total dose is less than 4 gm. during 6 weeks. Amphotericin B can be administered either parenterally (low initial dose gradually increased from 0.5 to a maximum of 1.5 mg./kg. per day)[2,5] or as a urinary tract irrigant. For local irrigation of a bezoar in the collecting system, it is prepared with 50 mg./l. sterile water and infused at 40 ml. per hour. Exposure to light for periods of less than 24 hours has shown no deleterious effect to the irrigant. However, for more prolonged exposure to light the irrigant container and lines should be protected.[23] With a retrograde ureteral catheter the bezoar can be bathed directly. Pressure in the system is controlled by a manometer with a pop-off mechanism at 20 cm. water to prevent extravasation, pyelovenous or pyelolymphatic reflux of agent or organisms. Toxicity with irrigation is minimal, since absorption across the urothelium is negligible.[3,24]

Empirically, rifampin enhances the in vitro antifungal activity of amphotericin B against Aspergillus and, therefore, it commonly is used in combination. Miconazole given systemically has had limited success in urinary tract infections owing to poor renal excretion and it should be considered only when amphotericin B is not tolerated. However, it has been shown to be a more cost-effective irrigant than amphotericin B, especially for nonbezoar candiduria.[25] Ketoconazole is an oral agent that has a broad spectrum of activity against yeasts but is less effective in systemic mycosis. It is limited in Aspergillus infections and is particularly ineffective in invasive disease. It is excreted poorly in the urine and is antagonistic to the effects of amphotericin B. Adverse effects are fewer than with miconazole but hepatotoxicity occurs in approximately 5% of the patients.[2]

Itraconazole is an investigational oral triazole with specific activity against Aspergillus. High tissue levels are obtained but urine levels are uncertain and are considered to be low. It is effective in disseminated mycosis but, until our case, it had not been used in renal bezoars. Toxicity has been negligible.[26,27]

Systemic medical treatment should be instituted immediately when systemic involvement is suspected or evidenced (fungemia, retinitis/endophthalmitis, radiological stigmata of pulmonary infiltration, diffuse mucocutaneous mycosis, positive spinal tap and so forth). Elevated candidal antigen titers may prove to be helpful to distinguish invasive candidiasis from disease limited to the urothelium.[28] For disease limited to the collecting system intravenous amphotericin B will be of negligible benefit and only those antifungals that have significant urinary levels should be used.

Access to the upper tracts is necessary in all cases of fungal bezoars to relieve obstruction, establish drainage and apply antifungal medication directly to the diseased site. In selected cases an open operation may be necessary for initial access, particularly if the condition has deteriorated such that more conservative endourological techniques would be ineffective. Otherwise, endourological access should be established either via a percutaneous nephrostomy tube or with directed irrigation through a ureteral catheter. The ideal antegrade irrigation should involve inflow to the collecting system through a mid or upper pole calix and outflow through a nephrostomy tube passed through an inferior pole posterior calix. The latter access makes possible an ideal tract that can be dilated for rigid nephroscopy and allows best access for potential debulking of the entire collecting system. If, after irrigation (either antegrade or retrograde), fungal cultures are negative and there is no evidence of filling defects on contrast studies, irrigation can be stopped and the catheters removed. However, obstructing lesions or bezoars that fail to show progressive resolution should have prompt, early surgical debulking by extraction and lavage. Rigid nephroscopy through the previously dilated nephrostomy tract and ureteroscopy are suited to this end. Rigid nephroscopy permits use of more substantial instruments than does flexible access. Tenacious, gummy bezoars, such as we found with Aspergillus, may be debulked with a cold loop resectoscope technique or forceps. Less dense and flocculent bezoars typical of Candida (especially C. glabrata) may be disrupted with direct mechanical agitation with various endourological instruments, such as a guide wire.[29] Before debulking, premedication with intravenous amphotericin B is recommended to avoid potential systemic dissemination of the fungus. Systemic amphotericin B should be continued in the immediate postoperative period until absence of fungemia is assured. After debulking, the upper tracts should be irrigated until urine cultures are negative and no radiological evidence of disease persists. Open pyelotomy and nephrectomy may be required if the disease progresses despite medical therapy and endourological debulking. Our algorithm for the surgical management of fungal bezoars is summarized in figure 4.

Our experience with 9 renal bezoars sharply contrasts the morbidity of the 2 fungal organisms reported. Aspergillus was considerably more morbid. The duration of hospitalization was markedly prolonged and significant complications were limited exclusively to this group. Of 6 renal units with aspergillomas 2 required nephrectomy, whereas all 3 Candida bezoars were managed successfully with a combination of medical and endourological therapy. It should be emphasized that both cases requiring nephrectomy had massive bulky Aspergillus bezoars, occupying essentially the entire collecting system. Although bilateral involvement was seen in all 3 patients with Aspergillus, all of the other 4 kidneys had small volume disease involving either a single calix or a portion of the renal pelvis. Each of these units was treated successfully with a combined therapeutic approach as noted previously. Likewise, all Candida bezoars were relatively small volume lesions.

During medical treatment urine surveillance specimens for culture and sensitivity testing must be obtained to ensure that resistant fungal organisms are appropriately recognized and treated. Our experience with amphotericin B-resistant Aspergillus and subsequent progression of disease requiring nephrectomy emphasizes this point. Investigational agents, such as itraconazole, are available on a protocol basis and, therefore,

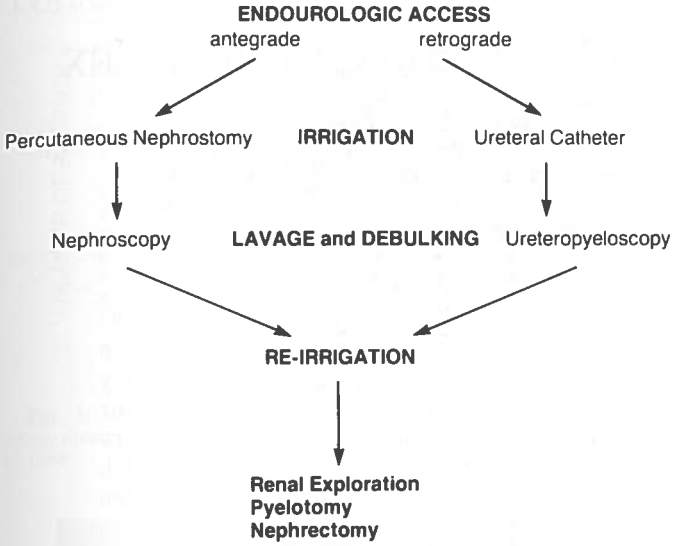

FIG. 4. Algorithm for surgical management of upper tract fungal bezoars.

close collaboration with the infectious disease consultation service is advised.

In limited disease involving only a small portion of the collecting system irrigation with amphotericin B after endourological access is indicated. Prompt debulking should be performed for large lesions filling the majority of the collecting system, especially when Aspergillus is the infecting organism. Medical therapy, including irrigation, should continue until radiographic clearance and microbiological eradication are demonstrated. When irrigation fails to result in clinical or radiographic improvement, early debulking should be done. The timing of debulking is a matter of clinical judgment but we favor intervention after 2 to 3 weeks of irrigation and systemic medical therapy if serial upper tract imaging fails to show evidence of clearing.

In conclusion, in immunocompromised patients, especially those with diabetes mellitus and filling defects of the upper urinary tract, one must maintain a high suspicion for fungal bezoars. Indeed, urologists should expect to encounter these diseases more frequently as we treat more and more critically ill patients. Their fragility dictates aggressive medical and endourological intervention. The over-all success of the treatment depends on this combined approach when neither medical nor surgical therapy alone is sufficient.

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