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Original Article

Cryptococcuria as a Manifestation of Disseminated Cryptococcosis and Isolated Urinary Tract Infection

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SUMMARY: Fungal infection of the genitourinary system is a relatively uncommon presentation. Cryptococcuria has rarely been recognized in clinical practice. Patients with positive urine culture for *Cryptococcus neoformans* from 1992 to 2003 were retrospectively reviewed. Sixteen patients were identified. Nine (56%) patients were male, with a mean age of 44 ± 21 (range, 16-88) years. Fifteen (94%) patients had underlying conditions such as HIV infection, diabetes mellitus, hypertension, and/or systemic lupus erythematosus. Thirteen (81%) patients had cryptococcuria as a manifestation of disseminated cryptococcosis, and the rest had only isolated cryptococcuria. Urinary analysis revealed proteinuria (75%), pyuria (31%), and budding yeast (13%). Nine (56%) patients received antifungal therapy. Other patients were misdiagnosed or died before treatment. The mortality rate was 64%. In conclusion, cryptococcuria is not extremely rare and can present as a manifestation of disseminated cryptococcosis or isolated urinary tract infection.

INTRODUCTION

Cryptococcosis, caused by *Cryptococcus neoformans*, is one of the most common opportunistic infections in HIV-infected patients (1). It occurs less frequently in other immunocompromised hosts (2). The clinical presentations of cryptococcosis vary depending on the host and site(s) of infection. The most commonly involved organs are lungs and the central nervous system (1). Fungal infection of the genitourinary system is a relatively uncommon presentation (3), and cryptococcal involvement of the genitourinary tract is not routinely documented. We aimed to describe the clinical characteristics of patients with positive urine culture for *C. neoformans* or cryptococcuria.

MATERIALS AND METHODS

Patients: We retrospectively reviewed the medical records of patients with positive urine culture for *C. neoformans* between January 1992 and December 2003. The data, including clinical features, underlying conditions, laboratory findings, clinical diagnosis, treatment, and outcome, were reviewed. Diagnosis of cryptococcal infection was based on a positive culture of urine, cerebrospinal fluid (CSF), blood, or other body fluids. Disseminated cryptococcosis means more than one site showed positive culture for *C. neoformans*.

Identification of *C. neoformans*: *C. neoformans* was identified based on the characteristic structural appearance of narrow-based budding yeast with capsules. Differentiation from *Candida* spp. was made by testing for urease production and lack of pseudohyphae when grown on chlamydo spore agar. Confirmation of *C. neoformans* was made by carbon and nitrogen assimilation by agar disc method. The presence of serum and CSF cryptococcal antigen were detected by means of the cryptococcal antigen latex agglutination system (CALAS; Meridian Diagnostic Inc., Cincinnati, Ohio, USA).

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RESULTS

During the 12-year study period, 16 patients tested positive for cryptococcuria. The overall incidence rate was 0.56 per 10,000 patients discharged from our hospital (an 800-bed medical school). Of these, nine (56%) patients were male, with mean age of 44 ± 21 (range, 16-88) years. Clinical characteristics of all patients are summarized in Table 1. Fifteen (94%) patients had underlying conditions, including HIV infection, diabetes mellitus, hypertension, cirrhosis, systemic lupus erythematosus, renal calculi, and/or chronic renal failure. Mean CD4 cell count of HIV-infected patients was 20 ± 5 (range, 8-35) cells/mm^3. None of the patients had any symptoms of urinary tract infection.

Thirteen (81%) patients had cryptococcuria as a manifestation of disseminated cryptococcosis. Of theses, 12 patients had simultaneously presented with disseminated cryptococcosis. Cryptococcuria in patient L occurred as an early manifestation, and led to the diagnosis and treatment of disseminated infection. Among patients, *C. neoformans* was recovered from blood (56%), CSF (50%), sputum (12%), lymph node (6%), cervical discharge (6%), and cutaneous papule (6%). Serum of CSF cryptococcal antigen was measured in two and three patients, respectively, with the titers ranging from 1:8 to 1:1024. Patient F, who tested negative for serum cryptococcal antigen, had only cryptococcuria without evidence of infection at other sites. Six (37%) patients had concomitant opportunistic infections including salmonellosis, tuberculosis, and *Pneumocystis carinii* pneumonia.

Urinary analysis showed wide range of abnormalities, such as proteinuria (75%), pyuria (31%), and hematuria (25%). Budding yeast was found only in two (13%) patients. Regard-

Table 1. Summary of clinical characteristics of 16 patients with cryptococcuria

Patients	Age, sex	Underlying condition(s)	Disseminated cryptococcosis	Other site(s) of positive cryptococcal culture	Cryptococcal antigen titer (body fluid)	Co-opportunistic infection	Antifungal treatment	Outcome
A	37, M	HIV	Yes	CSF	1:8 (CSF)	Salmonellosis	Itraconazole	Survived
B	34, M	HIV	Yes	Blood, CSF	–	–	–	Lost to follow up
C	26, M	HIV	Yes	Blood, CSF	1:1024 (CSF)	–	AmB	Survived
D	32, F	HIV	Yes	Blood, pus (cervix)	–	–	–	Died
E	28, F	HIV	Yes	Blood, CSF	1:256 (CSF)	–	AmB	Survived
F	32, M	HIV	No	–	Negative (serum)	PCP	–	Died
G	45, M	HIV	Yes	Blood	–	PCP	–	Died
H	56, F	HIV	Yes	Blood	Positive (serum)	Disseminated TB	Fluconazole	Survived
I	64, M	HIV, DM	Yes	Blood, CSF	–	Salmonellosis	AmB	Died
J	55, M	HIV, DM	Yes	Blood	–	–	AmB	Died
K	25, M	HIV, renal calculi	Yes	CSF, LN, cutaneous papule	–	TB pericarditis	AmB	Survived
L	76, M	Cirrhosis	Yes	CSF	–	–	AmB	Died
M	20, F	SLE	Yes	Blood, CSF, sputum	–	–	AmB	Died
N	68, F	HT	Yes	Sputum	–	–	–	Died
O	88, F	CRF	No	–	–	–	–	Died
P	16, F	None	No	–	–	–	–	Lost to follow up

AmB: amphotericin B, CSF: cerebrospinal fluid, CRF: chronic renal failure, DM: diabetes mellitus, HIV : human immunodeficiency virus, HT: hypertension, LN: lymph node, PCP : *Pneumocystis carinii* pneumonia, SLE: systemic lupus erythematosus, TB: tuberculosis.

ing renal function, mean blood urea nitrogen and creatinine were 27.3 ± 19.9 (range, 5-76) mg/dl and 1.7 ± 1.1 (range, 0.7-3.7) mg/dl, respectively.

Seven (44%) patients were treated with amphotericin B, and one patient each was treated with fluconazole and itraconazole. Seven (44%) patients were not treated with any antifungal drugs because five of them died and two were lost to follow up before receiving the results of cultures. Two (12%) patients had a recurrence of cryptococcal infection. The mortality rate was 64%. The causes of death were underlying diseases, disseminated cryptococcal infection, and/or concomitant opportunistic infections.

DISCUSSION

Infection caused by *C. neoformans*, an encapsulated yeast commonly associated with excreta of pigeons, produces a subacute and/or chronic infection and primarily involves the lungs (4). The yeast then hematogenously spreads to other organs of the body. Involvement of the genitourinary system is relatively uncommon (5,6). Cryptococcal infection of kidney (5,6), prostate gland (5-9), and epididymis (10) have been reported.

Our study showed that cryptococcuria could occur not only in HIV-infected patients but also in patients with other immunocompromised conditions. In addition, a young patient without underlying disease (patient P) was considered an apparently normal host. *C. neoformans* identified in the urine is suggested as a potential early indicator of disseminated disease (11). Cryptococcuria in our patients presented as part of disseminated cryptococosis in a high percentage, and almost all patients had simultaneously presented with cryptococcal meningitis or cryptococcemia. Interestingly, cryptococcuria in patient L occurred as an early event and led to the diagnosis of disseminated cryptococcosis including asymptomatic cryptococcal meningitis. Based on the high proportion of disseminated infection observed in the present study, we suggest that patients who present with cryptococcuria should be evaluated for systemic infection. Lumbar punctures should be performed. Blood culture and serum cryptococcal antigen test may be helpful.

None of our patients had any symptoms of urinary tract infection because they were truly asymptomatic and/or there was a lack of data due to the fact that this was a retrospective study. Urinary analysis of cryptococuria demonstrated a wide range of abnormalities and nonspecificity. Proteinuria ranging from 1+ to 4+ was found in a high percentage. Proteinuria might be caused by cryptococcuria itself or by other underlying conditions (e.g., diabetes mellitus, hypertension). Budding yeast was revealed at low percentages, though its presence was significant information. Proteinuria and/or budding yeast can be clues that cryptococcuria is present. In addition, a previous study suggested that cryptococcal antigen detection from urine specimens could be used for cryptococcal infection diagnosis (12). Urine cultures of these patients were performed as a basic investigation to evaluate the causes of fever. All positive urine cultures were routinely cultured for aerobic bacteria. The yield would have been higher if the laboratory had focused on recovery of fungi.

Only nine patients received specific therapy. Those who did not receive antifungal therapy died or were lost to follow-up before receiving the results of urine culture. The high mortality rate emphasizes that patients with cryptococcuria may have more advanced underlying disease or severe cryptococcal infection. There was a recurrence of infection in two patients. Apart from poor compliance, other reasons for such outcomes may include the lack of an adequate host response and persistent foci of infection. Regions in the urinary tract, such as the prostate, may be the focus from which dissemination occurs in recurrent cryptococcal disease (13).

The limitations of our retrospective study are lack of investigation of genitourinary system abnormalities, and no systematically conducted urinary analysis or urine culture to confirm treatment outcome. Studies of kidney parenchyma, prostate gland, and epididymis by appropriate means should

be conducted if feasible. Typing of cryptococcal varieties was not performed, so we can draw no conclusion about the relationship between cryptococcuria and the subtypes of the infecting isolate. Cryptococcal antigen titers in the bodily fluids including urine should be performed. Long-term follow-up after appropriate treatment is also required to determine the cure rate of this disease.

In conclusion, cryptococcuria can occur in both HIV- and non-HIV-infected patients with an immunocompromised condition. Cryptococcuria is not extremely rare and can present as a manifestation of disseminated cryptococcosis or isolated urinary tract infection. Proteinuria and presence of budding yeast on urinary analysis may be clues that cryptococcuria is present, and further investigation can lead to early diagnosis and treatment. Because the mortality rate is high, early detection and treatment are crucial to improve clinical outcome.

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