Torulopsis glabrata urinary tract infection treated with 5-fluorocytosine

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SYNOPSIS Two diabetic patients with symptomatic urinary tract infection by *Torulopsis glabrata* were successfully treated with two-week courses of 5-fluorocytosine.

After *Candida albicans*, *Torulopsis glabrata* is the yeast most commonly isolated from clinical material in a general laboratory (Mackenzie, 1961; Speller and Davies, 1973) though it is present more often in a colonizing than in a pathogenic role. Recently, however, there has been renewed interest in *T. glabrata* as an opportunistic pathogen (Marks, Langston, and Eickhoff, 1970). This report concerns two cases in which urinary tract infection with *T. glabrata* in diabetics gave rise to symptoms. Treatment of such infections may be difficult (Marks *et al*, 1970) but both these patients responded rapidly to short courses of 5-fluorocytosine (5FC).

Laboratory Methods

Approximate viable counts of yeasts in urine specimens were estimated by culture of 0.005 ml from a standard loop on Sabouraud's dextrose-peptone agar. Minimum inhibitory concentrations were determined by the method of Shadomy (1969) and serum and urinary concentrations of 5FC by a plate diffusion method, employing yeast morphology agar (Difco) and surface inoculation with a sensitive *C. albicans* isolate.

Case Histories

CASE 1

Mrs L.M., aged 59, presented in 1971 with pruritus vulvae, polyuria, and polydipsia, and was found to have diabetes mellitus, which was controlled by diet and oral hypoglycaemic agents. In August 1972 she complained of frequency and dysuria, and a mid-stream specimen of urine showed 80 leucocytes per high-power field in the centrifuged deposit, and yielded approximately 10^4 colonies per ml of *T. glabrata*.

Received for publication 10 October 1973.

Because the significance of this finding was not fully appreciated seven further urine specimens were sent during the ensuing six months, all of which showed marked pyuria, and yielded 10^4 to 10^6 per ml colonies of *T. glabrata* (fig 1). There was no significant bacterial growth on any occasion, and culture for mycobacteria was negative.

She was admitted for investigation and treatment in February 1973. Her blood urea was normal, but intravenous pyelography showed a left hydro-

Fig 1 Centrifuged deposit from urine of case 1 before treatment, showing yeasts and leucocytes. Gram stain.

nephrosis, and cystoscopy revealed mucosal polypi and gross injection of the bladder lining, with phosphatic debris. Her serum, tested at the Mycological Reference Laboratory, London School of Hygiene and Tropical Medicine, showed a strongly positive precipitin reaction with *T. glabrata* antigen (fig 2). A vaginal swab yielded a light growth of *T. glabrata*. The minimum inhibitory concentration of 5FC for the urinary isolates was 2.5 µg per ml.

Fig 2 Immunodiffusion reactions obtained with *T. glabrata* antigen (T) and sera of patients 1 (S1) and 2 (S2) (Mycological Reference Laboratory, London School of Hygiene and Tropical Medicine).

She was treated with 5FC, 150 mg/kg/day for four days, and then 50 mg/kg/day for 10 days. The yeasts were rapidly eradicated from her urine, with lessening of the pyuria and relief of her urinary symptoms. The concentrations of 5FC obtained in her serum and urine are set out in the table. She has

suffered no recurrence in the five months since her discharge from hospital.

CASE 2

Mrs L.G., aged 71, was admitted as an emergency with acute retention of urine, after a short history of dysuria, frequency, and haematuria. A catheter specimen of urine showed more than 100 leucocytes per high-power field and many red cells in the centrifuged deposit, and yielded a growth of more than 10^5 colonies per ml of *T. glabrata*. No bacteria were isolated. These findings were confirmed with two subsequent urine specimens, three days and seven days later. She was found to be diabetic and was treated with diet and insulin. Serological tests for *T. glabrata* were negative (fig 2). The minimum inhibitory concentration of 5FC for the *T. glabrata* isolates was 0.1 µg per ml.

She received 5FC, with the same dosage regimen as case 1, and the yeasts quickly cleared from her urine. Serum and urine concentrations of 5FC are shown in the table. Subsequently her urine became infected with *Escherichia coli* but there was no recurrence of the yeast infection. She required a below-knee amputation for spreading gangrene from a penetrating ulcer of the heel and died from a massive pulmonary embolus.

Comment

In these two diabetic patients *T. glabrata* was repeatedly isolated alone, and in significant numbers (10^4 per ml or more) from urine specimens with marked pyuria, and in both patients definite symptoms were associated with the infection. The first patient had strongly reacting antibodies to the organism in her serum, a result of the chronic infection, with probable upper urinary tract involvement while the second patient had an acute presentation with lower urinary tract infection and no detectable antibody response. Neither patient had had previous urethral catheterization or antibacterial treatment,

Case	Day of treatment	Daily Dose (mg/kg)	Eight-hourly Dose (gm)	5FC Concentration		
				Serum (µg/ml)		Urine (mg/ml)
				Two Hours after Dose	Four Hours after Dose	
1	2nd	150	3.5	94	63	5.8
	4th	150	3.5	75	78	5.3
	10th	50	1.25	35	30	1.9
2	2nd	150	2.25	55	—	5.4
	8th	50	0.75	26	—	0.9

Table 5-fluorocytosine concentrations in serum and urine

which predispose to colonization by *T. glabrata* among other yeasts (Marks *et al*, 1970).

In this department *T. glabrata* was found in 82 of 234 midstream and catheter urines yielding 10^4 or more colonies per ml of yeasts (Speller and Davies, 1973) and it is likely that infection by this organism is commoner than has been thought. Ahearn, Jannach, and Roth (1966) isolated *T. glabrata* from 45 of 1013 urine specimens and noted that nine of the patients had diabetes mellitus. The association with diabetes has been noted by others (Guze and Haley, 1958; Edebo and Spetz, 1965; Marks *et al*, 1970) and Hasenclever and Mitchell (1962) showed increased multiplication of *T. glabrata* in the kidneys of mice when they were made diabetic with alloxan. Marks *et al* (1970) isolated *T. glabrata* from the urine of 22 patients, and found chronic infection in two, which did not respond to amphotericin B bladder washouts.

Of 153 isolates of *T. glabrata* tested in this department (Speller and Davies, 1973), 152 were inhibited by $1\ \mu\text{g}$ 5FC per ml or less, and the single moderately resistant isolate had a minimum inhibitory concentration of $31\ \mu\text{g}$ per ml—a concentration greatly exceeded in the urine of these patients throughout treatment. Others have reported more primarily resistant isolates of *T. glabrata* (Hamilton-Miller, 1972; Steer, Marks, Klite, and Eickhoff, 1972). 5-Fluorocytosine has been used with success in urinary infection by *Candida albicans* (Davies and Reeves, 1971; Schönebeck, Steen, and Tärnvik, 1972; Holt and Newman, 1973) though treatment sometimes fails. One case of successful treatment of *T. glabrata* septicaemia has been recorded (Webb, Speller, and Buckler, 1970). The two patients described here were rapidly cured. No resistant strains emerged, perhaps because the drug was given in a high dose, which produced massive urinary concentrations, at the beginning of the course of treat-

ment. No adverse effects were observed during the treatment of these patients; in particular their blood counts and liver function tests remained normal.

I am indebted to Dr M. Hartog and Professor J. H. Peacock for permission to describe these patients, to Dr Mary P. English for assistance with yeast identification, to Miss Christine Philpot for the serological tests, and to Mr D. M. Bruten and the Department of Medical Illustration, Bristol Royal Infirmary, for the photographs. 5-Fluorocytosine was provided by Dr J. Garrod of Roche Products Ltd.

References

- Ahearn, D. G., Jannach, J. R., and Roth, F. J., Jr. (1966). Speciation and densities of yeasts in human urine specimens. *Sabouraudia*, **5**, 110-119.
- Davies, R. R., and Reeves, D. S. (1971). 5-Fluorocytosine and urinary candidiasis. *Brit. med. J.*, **1**, 577-579.
- Edebo, L., and Spetz, A. (1965). Urinary tract infection with *Torulopsis glabrata* treated by alkalization of urine. *Brit. med. J.*, **2**, 983-984.
- Guze, L. B., and Haley, L. D. (1958). Fungus infections of the urinary tract. *Yale J. Biol. Med.*, **30**, 292-305.
- Hamilton-Miller, J. M. T. (1962). A comparative *in vitro* study of amphotericin B, clotrimazole and 5-fluorocytosine against clinically isolated yeasts. *Sabouraudia*, **2**, 276-283.
- Hasenclever, H. F., and Mitchell, W. O. (1962). Pathogenesis of *Torulopsis glabrata* in physiologically altered mice. *Sabouraudia*, **2**, 87-95.
- Holt, R. J., and Newman, R. L. (1973). The antimycotic activity of 5-fluorocytosine. *J. clin. Path.*, **26**, 167-174.
- Mackenzie, D. W. R. (1961). Yeasts from human sources. *Sabouraudia*, **1**, 8-15.
- Marks, M. I., Langston, C., and Eickhoff, T. C. (1970). *Torulopsis glabrata*—an opportunistic pathogen in man. *New Engl. J. Med.*, **283**, 1131-1135.
- Schönebeck, J., Steen, L., and Tärnvik, A. (1972). 5-Fluorocytosine treatment of *Candida* infections of the urinary tract and other, sites. *Scand. J. Urol. Nephrol.*, **6**, 37-43.
- Shadomy, S. (1969). *In vitro* studies with 5-fluorocytosine. *Appl. Microbiol.*, **17**, 871-877.
- Speller, D. C. E., and Davies, M. C. (1973). Sensitivity of yeasts to 5-fluorocytosine. *J. med. Microbiol.*, **6**, 315-321.
- Steer, P. L., Marks, M. I., Klite, P. D., and Eickhoff, T. C. (1972). 5-fluorocytosine—an oral antifungal compound. *Ann. intern. Med.*, **76**, 15-22.
- Webb, A. J., Speller, D. C. E., and Buckler, K. G. (1970). *Torulopsis glabrata* septicaemia treated with 5-fluorocytosine. *Lancet*, **1**, 839-840. (L).