J. Hyg., Camb. (1977), 78, 129
Printed in Great Britain

Torulopsis glabrata infections in Singapore: a 4-year study

BY ROWLAND J. S. TAN AND EK-WANG LIM
Department of Microbiology, Faculty of Medicine, University of Singapore, Sepoy Lines, Singapore, 3, Republic of Singapore
AND HOCK-KIN TEO
Department of Pathology, Singapore General Hospital, Ministry of Health, Outram Road, Singapore 3, Republic of Singapore

(*Received* 20 *June* 1976)

SUMMARY

During the period 1971–4, *Torulopsis glabrata* formed 42% of yeasts isolated from 5677 clinical specimens from patients with cancers, diabetes mellitus, chronic renal failure, pregnancy or major surgical operations complicated by mycotic infections. The significance of *T. glabrata* in these patients is discussed.

INTRODUCTION

Torulopsis glabrata is a yeast-like micro-organism with globose, ovoid-to-elongated cells. It reproduces by multipolar budding but fails to produce septate hyphae or ascospores. On Sabouraud dextrose agar the colonies are white or cream-coloured and have no carotenoid pigments (Kockova-Kratochvilova, 1973). *Torulopsis* is a distinct genus and together with *Candida* and *Cryptococcus* is placed under the subfamily of *Cryptococcoideae*.

Like *Candida albicans*, *T. glabrata* is widely distributed in man and animals. For many years this micro-organism was thought to be a saprophyte. However, in 1937 Black & Fisher reported the association of *T. glabrata* with broncho-pneumonia. Since then, many reports have been published on the implication of *T. glabrata* in fungaemia, pulmonary and urinary tract infections (Aisner *et al.* 1974; Melnick & Smith, 1974; Kauffman & Tan, 1974).

The incidence and significance of *T. glabrata* in patients with clinical mycoses in Singapore was hitherto unknown. Therefore its pathogenic role in relation to many major underlying diseases still remains obscure. This paper describes the isolations of *T. glabrata* from clinical specimens and discusses its significance in these patients with clinical mycoses in Singapore during a 4-year period between 1971 and 1974.

MATERIALS AND METHODS

All the clinical specimens received at the Mycology Laboratory were immediately streaked on Sabouraud dextrose agar with and without chloramphenicol and cycloheximide. The plates or slants were incubated at room temperature (25 °C)

or 2 days before they were read. Strains isolated were inoculated into fermentation and assimilation tubes according to the method described by Silva-Hutner & Cooper (1974). Those strains suspected of being *T. glabrata* were also streaked on blood agar.

T. glabrata ferments only glucose and assimilates glucose and trehalose. On blood agar, it produces small white to cream-coloured colonies approximately 0·5–1·5 mm in diameter as compared to *Candida albicans* which produces large white colonies about 3·0–4·0 mm in diameter. Microscopic examination reveals globose-to-ovoid cells with no ascospores or pseudohyphae. The small colonies on blood agar and the characteristic sugar fermentation and assimilation patterns clearly distinguish *T. glabrata* from other yeasts.

Two local strains of *T. glabrata* (P 25 and F 125) were confirmed by Dr D. W. R. Mackenzie of the Mycological Reference Laboratory, London School of Hygiene and Tropical Medicine, England.

RESULTS

A summary of yeast isolations during the period 1971–4 is shown in Table 1. The number of yeast isolations increases quite dramatically from 307 in 1971 to 940 in 1974 (an increase from 21 % to 80 %). This is particularly so for *Candida* species, *Saccharomyces cerevisiae* and *Torulopsis glabrata*. The latter registered a fourfold increase from 111 positives in 1971 to 402 positives in 1974, i.e. an increase from 7·6 % to 34·0 % of the total specimens processed (though the number of specimens processed in 1973 and 1974 were less than those in 1971 and 1972).

Table 2 shows a summary of *T. glabrata* isolations from clinical specimens during the period 1971–4. Cervical/vaginal swabs, stool, urine, sputum and throat swabs accounted for most of *T. glabrata* isolates. Almost all the cervical/vaginal swabs were from patients attending the outpatient, maternity or family planning clinics throughout the country. The common disorders amongst these patients were vaginal discharges, vaginitis with and without pruritus and cervicitis. Patients attending the maternity clinics consisted mostly of pregnant women undergoing antenatal care with a small proportion undergoing post-natal education. Family planning clinics comprised women undergoing some form of birth control including those on the Pill.

Most of the *T. glabrata* isolations from other clinical specimens were from patients with major underlying diseases. Nine strains of *T. glabrata* isolations from urine specimens were from patients with primary urinary tract infections complicated by diabetes mellitus. The remaining *T. glabrata* isolations from urine specimens were from patients with chronic renal diseases.

All the six strains from blood were from patients with terminal cancers. Positive cultures from throat swabs and sputums came from patients with lymphomas, *nasopharyngeal carcinomas and lung cancers. Positive cultures from stools were* usually associated with gastroenterological disorders with or without surgical intervention.

Table 1. *Summary of yeast isolations between* 1971 *and* 1974

	1971	1972	1973	1974	Total	%
Total specimens processed	1452	1789	1257	1179	5677	—
Candida species	157	384	393	447	1381	48·9
Saccharomyces cerevisiae	11	32	35	40	118	4·2
Torulopsis glabrata	111	320	359	402	1192	42·2
Geotrichum species	10	15	5	6	36	1·3
Cryptococcus neoformans	11	2	14	25	52	1·8
Rhodotorula species	7	15	2	20	44	1·6
Total yeast isolates	307	768	808	940	2823	100·0
% of *T. glabrata* over total specimens processed	7·6	17·9	28·6	34·0	21·0	
% of *T. glabrata* over total yeast isolates	36·2	41·7	44·4	42·8	42·2	

Table 2. *Summary of* Torulopsis glabrata *isolations from clinical specimens*

	1971	1972	1973	1974	Total	%
Throat swab	10	50	46	44	150	12·6
Sputum	8	23	—	13	44	3·7
Skin scraping	—	13	3	7	23	1·9
Gastric lavage	—	5	4	—	9	0·8
Nail scraping	—	6	3	2	11	0·9
Blood	—	1	3	2	6	0·5
Wound	—	11	2	—	13	1·1
Urine	5	12	28	48	93	7·8
Stool	38	87	77	82	284	23·8
Cervical/vaginal swab	50	112	193	204	559	46·9
Total	111	320	359	402	1192	100·0

DISCUSSION

In 1957, Wickerham was the first to report on the increase in frequency of *T. glabrata* infections from clinical specimens in his mycological laboratory. Stenderup & Pederson (1962) also revealed a sharp increase in the isolations of *T. glabrata* from a series of routine hospital cultures. The incidence of *T. glabrata* was 14% of 968 positive yeasts isolated from clinical specimens.

Results from our 4-year study also indicate the increasing importance of *T. glabrata* infections in Singapore, as shown by the dramatic increase of *T. glabrata* isolations from clinical specimens from 7·6% to 34%. This rapid increase is probably due to our increasing awareness in recent years of this organism in clinical specimens.

The importance of pre-disposing factors in a variety of human and experimental mycoses is well documented (Grimley, Wright & Jennings, 1965; Sheldon & Bauer, 1962). The presence of these factors invariably contributed significantly to the manifestation of clinical disease which would not have been expressed under normal circumstances (Grimley *et al.* 1965).

From our study, *T. glabrata* infection is an important complication of diabetes mellitus. We found that nine of the patients with primary urinary tract infections,

and in which urine specimens yielded *T. glabrata*, were diabetics. No clinical records were available for follow-up studies. Nevertheless, the fact that *T. glabrata* was persistently isolated from repeat urine specimens strongly suggests that it was responsible for the urinary tract infections.

Speller (1974) reported two cases of diabetes mellitus complicated by *T. glabrata* urinary tract infections. Both were successfully treated with 5-fluorocytosine. Guze & Haley (1958) demonstrated *T. glabrata* in the urine of seven patients in a retrospective study of 1500 infected urine cultures. Four of the patients had diabetes mellitus. Edebo & Spetz (1965) also reported a case of urinary tract infection caused by *T. glabrata*. The patient was also a diabetic and was treated by increasing the pH of the urine with sodium citrate. Diabetes mellitus was also the pre-disposing factor in *T. glabrata* fungaemia. Katz & Pickard (1967) reported a case of a woman patient with systemic fungaemia complicated by diabetes mellitus.

The association of diabetes mellitus may be likened to the situation seen in phycomycete infections, such as mucormycosis as reported by Baker (1960). Hyperglycaemia in diabetes mellitus has been shown to inhibit phagocytosis by polymorphonuclear leukocytes, and acidosis may further contribute to these defects (Perille, Nolan & Finch, 1962; Bybee & Rogers, 1964; Bagdade, Nielson, Root & Bulger, 1970). Under such circumstances, it is no wonder that a *T. glabrata* infection is enhanced which, under normal conditions, would undoubtedly be arrested.

Isolations of *T. glabrata* from stools, throat swabs/sputa, urines, blood and gastric lavage constituted more than half of all the positive cultures in this study. Most of these were from patients with major underlying diseases such as cancers (lymphomas, leukaemias and nasopharyngeal carcinomas) and renal failures or from patients who had undergone major surgical operations. The high incidence of *T. glabrata* from this category of patient strongly indicates the important role of cancer as a pre-disposing factor in clinical mycoses in Singapore. This is well illustrated by the persistent recovery of *T. glabrata* from the blood of six leukaemic patients (Table 2).

Hutter & Collins (1962) also found an increased incidence of mycotic infections in their patients suffering from cancers (leukaemias and lymphomas) and concluded that the systemic mycosis was a major, if not the sole factor, in causing death. Baker (1962) also reported a 15% incidence of mycotic infections in his autopsy review of 261 leukaemic patients. Louria *et al.* (1967) demonstrated *T. glabrata* from blood cultures and ascitic fluid of a patient with advanced and metastasizing carcinoma. Melnick & Smith (1974) reported a case of a cancer patient with *T. glabrata* fungaemia through long-term use of hyperalimentation.

We also found that patients who had undergone major surgical operations were more prone to *T. glabrata* infections. This is evident from the recovery of *T. glabrata* from stools, gastric lavage and post-operative wounds of patients with gastroenterological disorders which required surgical intervention. Invariably, this category of patients received chemotherapy including antibiotics and steroids.

The role of chemotherapy in the aetiology of clinical mycoses is well known

(Torack, 1957; Sharp, 1954; McVay & Sprunt, 1951; McGovern *et al.* 1953). Antibiotics, by removing bacterial flora, facilitate fungal growth and proliferation. Steroids alter leucocyte response and depress immune reactions. Torack (1957) studied 13 cases of mycoses associated with antibiotic and steroid therapy and found that the use of antibiotics enhanced surface proliferation of fungi whilst combinations of antibiotics and steroids encouraged fungal invasion into deeper tissues and organs. Grimley *et al.* (1965) reported two cases of *T. glabrata* infections in patients with malignant diseases treated with various chemotherapeutic agents. In one case, yeast was recovered from the blood stream and urine, and was cultured from kidney specimens at autopsy. *T. glabrata* was also demonstrated histologically from various organs.

Our study of clinical mycoses in hospital patients suggests that *T. glabrata* is an opportunistic yeast which exists as a saprophyte under normal circumstances. However, in the presence of pre-disposing factors such as cancers, renal failures, diabetes mellitus, pregnancy or major surgical operations, *T. glabrata* is able to exert itself as a pathogen. The localization of *T. glabrata* in the gastro-intestinal and genito-urinary tracts invariably provides a convenient source of endogenous infection (Stenderup & Pederson, 1962). This observation seems to agree with similar studies undertaken in other countries (Hutter & Collins, 1962; Marks, Langston & Eickhoff, 1970; Speller, 1974).

We wish to express our appreciation to Dr Moses Yu, Chief Pathologist, Department of Pathology, Ministry of Health, Republic of Singapore, for access to all the clinical data presented in this paper. We are indebted to Dr D. W. R. Mackenzie of the Mycological Reference Laboratory, London School of Hygiene and Tropical Medicine, England, for confirming our *T. glabrata* isolates.

REFERENCES

Aisner, J., Sickles, E. A., Stephen, C., Schimpff, S. C., Young, V. M., Greene, W. H. & Wiernik, P. H. (1974). *Torulopsis glabrata* pneumonitis in patients with cancer. Report of 3 cases. *Journal of the American Medical Association* **230**, 584.

Bagdade, J., Nielson, K., Root, R. & Bulger, R. (1970). Host defence in diabetes mellitus: the feckless phagocyte during poor control and ketoacidosis. *Clinical Research* **18**, 181.

Baker, R. D. (1960). Diabetes and mucormycosis. *Diabetes* **9**, 143.

Baker, R. D. (1962). Leukopenia and therapy in leukaemia as factors predisposing to fatal mycoses. *American Journal of Clinical Pathology* **37**, 358.

Black, R. A. & Fisher, C. V. (1937). Cryptococcic bronchopneumonia. *American Journal of Diseases in Children* **54**, 81.

Bybee, J. D. & Rogers, D. E. (1964). The phagocytic activity of polymorphonuclear leukocytes obtained from patients with diabetes mellitus. *Journal of Laboratory and Clinical Medicine* **64**, 1.

Edebo, L. & Spetz, A. (1965). Urinary tract infection with *Torulopsis glabrata* treated by alkalization of urine. *British Medical Journal* ii, 983.

Grimley, P. M., Wright, L. D. & Jennings, A. E. (1965). *Torulopsis glabrata* infection in man. *American Journal of Clinical Pathology* **43**, 216.

Guze, L. B. & Haley, L. D. (1958). Fungus infections of the urinary tract. *Yale Journal of Biology and Medicine* **30**, 292.

Hutter, R. V. P. & Collins, H. S. (1962). The occurrence of opportunistic fungus infections in a cancer hospital. *Laboratory Investigation* **11**, 1035.

Katz, D. & Pickard, R. E. (1967). Systemic *Torulopsis glabrata* infection causing shock, fever and coma. *American Journal of Medicine* **43**, 151.

Kauffman, C. A. & Tan, J. S. (1974). *Torulopsis glabrata* renal infection. *American Journal of Medicine* **57**, 217.

Kockova-Kratochvilova, A. (1973). Comparative taxonomy of the Genus *Torulopsis* Berlese. *The Journal of General Microbiology* **79**, 239.

Louria, D. B., Blevins, A., Armstrong, D., Burdick, R. & Lieberman, P. (1967). Fungemia caused by nonpathogenic yeasts. *Archives of Internal Medicine* **119**, 247.

Marks, M. I., Langston, C. & Eickhoff, T. C. (1970). *Torulopsis glabrata* – an opportunistic pathogen in man. *New England Journal of Medicine* **283**, 1131.

McGovern, J. J., Parrott, R. H., Emmons, C. W., Ross, S., Burke, F. G. & Rice, E. C. (1953). The effect of aureomycin and chloramphenicol on the fungal and bacterial flora of children. *New England Journal of Medicine* **248**, 397.

McVay, L. V. & Sprunt, D. H. (1951). A study of moniliasis in aureomycin therapy. *Proceedings of the Society for experimental Biology and Medicine* **78**, 759.

Melnick, S. & Smith, D. E. (1974). *Candida tropicalis* and *Torulopsis glabrata* fungemia in a patient treated with long term hyperalimentation. *American Surgeon* **40**, 190.

Perille, P. E., Nolan, J. P. & Finch, S. C. (1962). Studies of the resistance to infection in diabetes mellitus: local exudative cellular response. *Journal of Laboratory and Clinical Medicine* **59**, 1008.

Sharp, J. L. (1954). The growth of *Candida albicans* during antibiotic therapy. *Lancet* i, 390.

Sheldon, W. H. & Bauer, H. (1962). The role of disposing factors in experimental fungus infections. *Laboratory Investigation* **11**, 1184.

Silva-Hutner, M. & Cooper, B. H. (1974). Medically important yeasts. In *Manual of Clinical Microbiology*, 2nd ed. (ed. E. H. Lennette, E. H. Spaulding and J. P. Truant), p. 491. American Society for Microbiology, U.S.A.

Speller, D. C. E. (1974). *Torulopsis glabrata* urinary tract infection treated with 5-fluorocytosine. *Journal of clinical Pathology* **27**, 50.

Stenderup, A. & Pederson, G. T. (1962). Yeasts of human origin. *Acta pathologica et microbiologica scandinavica* **54**, 462.

Torack, R. M. (1957). Fungus infections associated with antibiotic and steroid therapy. *American Journal of Medicine* **22**, 872.

Wickerham, L. J. (1957). Apparent increase in frequency of infections involving *Torulopsis glabrata* – procedure for its identification. *Journal of the American Medical Association* **165**, 47.