

Case report

Torulopsis glabrata fungaemia

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Opportunistic yeast infections have emerged as an increasing problem in immunocompromised and debilitated patients. Although *Candida albicans* is the yeast most commonly isolated from the body and that which most commonly causes candidiasis, several reports have documented the emergence of *Torulopsis glabrata* as an important pathogen. We describe cases of fungaemia caused by this yeast in compromised patients which illustrate noteworthy predispositions.

CASE 1

A female child with a birth weight of 919 g was born by premature normal delivery at 25 weeks gestation and was transferred to a neonatal intensive care unit. Respiratory distress syndrome developed and mechanical ventilation was commenced. Total parenteral nutrition was administered via peripheral venous cannulae. An eight day prophylactic course of penicillin and gentamicin had been commenced at birth. Following the isolation of coagulase negative staphylococci from peripheral venous blood culture and accompanying signs of clinical sepsis, a further 22 days of flucloxacillin and netilmicin was given. The clinical response was poor despite *in vitro* sensitivity of the micro-organism. Her respiratory secretions were colonised with *Pseudomonas spp.* and when clinical pulmonary infection developed, the drug regimen was changed to ceftazidime. Her clinical deterioration continued and one day later splenomegaly was noted and the platelet count fell further to $80 \times 10^9/l$.

Four sets of blood cultures and urine grew *Torulopsis glabrata* and she was commenced on amphotericin 1 mg/kg/day and flucytosine 80 mg/kg/day. During the next week there was no clinical response and amphotericin and flucytosine doses were progressively increased to 2 mg/kg/day and 160 mg/kg/day respectively. Her clinical condition improved and the platelet count rose steadily to $160 \times 10^9/l$. A total of 21 days antifungal therapy was administered, during which liver and renal function remained within normal limits and she subsequently made satisfactory progress.

CASE 2

A 74-year-old drowsy and dehydrated woman was admitted to a geriatric medical unit with increasing confusion, and urinary incontinence. She had poorly controlled non insulin dependent diabetes mellitus, ischaemic heart disease,

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cerebrovascular disease and mild dementia. The plasma glucose level was 56 mmol/l, white cell count $21 \times 10^9/l$, and serum urea 26.5 mmol/l. Intensive therapy with insulin, fluids and diuretics was commenced, and oral ampicillin 500 mg four times daily. A urinary catheter was passed to monitor output. She was slow to respond and hyperglycaemia persisted in spite of this treatment. After ten days she developed abdominal distension and signs of subacute obstruction. The antibiotic regimen was changed to cephradine and metronidazole. Direct microscopy of a catheter specimen of urine showed a white cell count > 1000 cells/cu mm, and yeasts were seen in large numbers.

The peripheral blood white cell count rose from 17 to $23 \times 10^9/l$. All antibiotics were stopped and intravenous amphotericin commenced at a dose of 0.3 mg/kg/day which was increased to 0.5 mg/kg/day after two days. *Torulopsis glabrata* was isolated from urine and three sets of blood cultures. There was a slow clinical improvement, accompanied by a slight fall in blood urea and creatinine levels and a normalisation of blood glucose. Amphotericin was continued for 11 days, by which time she was considered clinically to be no longer septicaemic. Catheter specimens of urine were clearer but some yeasts were still seen on microscopy. Unfortunately intractable congestive cardiac failure and right basal pulmonary consolidation led to death 34 days after admission.

CASE 3

A 60-year-old woman was admitted to hospital with a large perforated gastric ulcer. A partial gastrectomy was performed and she was commenced on mezlocillin and metronidazole. Postoperatively the patient was pyrexial, and amoxicillin was substituted for mezlocillin, with netilmicin added. A subclavian central venous catheter and an arterial catheter were inserted and the patient required assisted ventilation in a respiratory intensive care unit. Ten days postoperatively the gastroduodenostomy anastomosis failed and the abdominal wound burst, requiring emergency repair. A tracheostomy was also performed. Over the succeeding eight weeks the clinical course was stormy with a persistently spiking pyrexia, bile drainage, respiratory difficulty, depressed level of consciousness and a progressive flaccid peripheral motor neuropathy.

During this period clavulanate potentiated ampicillin, azlocillin and ceftazidime were successively prescribed while netilmicin and metronidazole were administered almost continuously. *Candida albicans* was first isolated from a catheter specimen of urine four days after admission and was subsequently isolated intermittently from sputum and wound swabs. Morphologically different yeasts, initially reported as "non pathogenic", were first isolated from a wound swab on day 15 and from sputum ten days later. Sixty days after admission her temperature rose to 40°C and two sets of blood cultures grew yeasts which were identified as *Torulopsis glabrata*. Culture of the subclavian catheter tip, removed two days later also yielded this organism. Amphotericin therapy 1.5 mg/kg on alternate days was given. The patient became afebrile after 24 hours and remained so. Treatment was continued for eight days at which time netilmicin and metronidazole were also stopped. The urinary catheter was removed 12 days later, and she was discharged 21 weeks after admission.

CASE 4

A 42-year-old man presented with small bowel infarction which was treated by resection followed by jejunostomy. Thereafter he was maintained on total parenteral nutrition. He suffered repeated episodes of coagulase negative

staphylococcal infection related to central venous catheters over a period of four months. These were treated by various antibiotics and replacement of the lines. A mild fungaemia in which *Candida albicans* was isolated from blood and catheter culture responded to removal of the catheter without antifungal therapy. A tunnelled venous catheter was inserted to allow continued parenteral feeding. Three days later he became profoundly septicaemic and hypotensive. *Torulopsis glabrata* was isolated from four sets of blood cultures and also from the catheter following its removal. Low dose amphotericin (0.5 mg/kg/day) and full dose flucytosine were commenced. After one week amphotericin dosage was increased gradually to 1.5 mg/kg/day and the patient responded temporarily but continued to show intermittent pyrexia of 38.5°C. Antifungal therapy continued for three weeks after which time he appeared stable and afebrile, but he died from bronchopneumonia two weeks later.

DISCUSSION

Torulopsis berlese, the name first coined by Berlese in 1884 included a number of yeast species. *Torulopsis glabrata* was first recognised by Anderson in 1917¹ and was thought to be a species of *Cryptococcus* because it produced no ascospores or hyphae. *T. glabrata* grows on routine bacteriological diagnostic culture media. Unlike *Candida spp.* the genus *Torulopsis* is distinguished by the complete absence of hyphal or pseudohyphal forms under all cultural conditions because it reproduces by budding only. The assimilation of trehalose and glucose but not other sugars confirms the identity,² but because of its close antigenic relationship to *Candida* it is often identified as "Candida species/non albicans" on the basis of germ tube tests. The organism is sensitive to amphotericin and normally also to flucytosine, but it is generally resistant to ketoconazole. Susceptibility to miconazole is variable, up to 40% of strains being resistant.³

T. glabrata was formerly considered to be wholly saprophytic but has become increasingly recognised as an opportunistic pathogen in the altered host. Like *Candida spp.* it may be found as a commensal in the gastrointestinal, respiratory and genitourinary tracts of normal individuals. Particularly at risk are those who have undergone major gastrointestinal surgery requiring prolonged intravenous feeding, have had broad spectrum antibiotics, diabetics, or immunocompromised patients.

The spectrum of infection ranges from mild fungaemia to endocarditis,⁴ pyelonephritis,⁵ pneumonitis,⁶ and peritonitis.⁷ The compromised host is particularly liable to tissue invasion and metastatic infected foci. Experimental pathogenicity studies on *T. glabrata* have demonstrated that the yeast does not produce a progressive infection in normal mice, but the capacity for tissue invasion was enhanced in steroid-treated, alloxan-diabetic and irradiated mice.⁸ Normal human plasma inhibits the growth of *T. glabrata* more than other yeasts *in vitro*, the inhibitory factor being a combination of transferrin, IgM and other unidentified proteins.⁹ The clinical presentation is undistinguishable from systemic candidosis, and can vary from an indolent low grade pyrexia to profound septicaemia with shock.

The first case illustrates the pathogenic potential of the yeast in a very pre-term neonate. Multiple invasive procedures, the prescription of broad spectrum antibiotics over a long period along with intravenous feeding enabled the organism to invade systemically. A very high dose antifungal regimen was required to produce a clinical cure. This was tolerated well by the infant, with no

evidence of renal or haematological toxicity. Case two became fungaemic following urinary catheter colonisation. Impaired renal function does not demand a reduction in amphotericin dosage since only 3% is excreted in the urine.¹⁰ However, low dosage regimens are being increasingly used to reduce toxicity, particularly when the drug is used in combination with flucytosine. Since flucytosine is mainly excreted through the kidneys, the addition of this drug is particularly appropriate in treating fungaemia associated with renal tract infection. The regimen has been combined with local instillations of amphotericin into the bladder,⁵ but bladder colonisation cannot be eradicated without catheter removal. Poor diabetic control adds to the difficulties of treatment since hyperglycaemia and acidosis interfere with polymorphonuclear phagocytosis.¹¹

The third and fourth cases represent typical examples of initial colonization of a central venous catheter and subsequent fungaemia due to the yeast after gastrointestinal surgery, prolonged antibiotic therapy and intravenous feeding. Removal of intravenous catheters and subsequent alternate day treatment with amphotericin alone for 10 days was successful in rapidly eradicating the infection in case three. Case four showed spontaneous recovery following removal of the central catheter, but general deterioration compromised his ability to respond to the subsequent *T. glabrata* septicaemia. Metastatic seeding may have occurred prior to diagnosis or to catheter removal, or to the establishment of therapeutic antifungal serum concentrations. Such events are often only diagnosed at post-mortem. Systemic infection with *T. glabrata* is a life-threatening event in the metabolically or immunologically compromised patient. It is particularly likely to occur following broad spectrum antibacterial therapy or to the prophylactic or therapeutic administration of imidazoles.

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