Chronic Urinary Tract Infection Due to *Candida utilis*

Kevin C. Hazen, Gordon W. Theisz and Susan A. Howell

Chronic Urinary Tract Infection Due to Candida utilis

KEVIN C. HAZEN,1* GORDON W. THEISZ,1 AND SUSAN A. HOWELL2†

Division of Clinical Microbiology, Department of Pathology, University of Virginia Medical Center, Charlottesville, Virginia 22908,1 and Department of Microbial Diseases, St. John’s Institute of Dermatology, St. Thomas’ Hospital, London, England2

Received 28 September 1998/Returned for modification 21 October 1998/Accepted 11 November 1998

An elderly male was seen at an outpatient urology clinic over a period of 3 years with repeat urine specimens containing 10^4 to 10^5 CFU of a “Candida species, not C. albicans.” The urine specimens were described as infected due to the presence of pyuria, but no antifungal therapy was administered. On two occasions, the patient presented to the emergency room and urine specimens were sent to the clinical microbiology laboratory. On both occasions, a yeast was isolated at concentrations of >10^8 CFU/ml. The organism was identified as the anamorphic yeast Candida utilis (teleomorph: Pichia jadinii) by conventional methods. Molecular methods, including karyotyping and restriction enzyme analysis, confirmed that the isolates were identical and were C. utilis. The patient developed benign prostatic hypertrophy and chronic obstructive pulmonary disease during the 3-year course. This report is the first demonstration of the isolation of the industrially important yeast C. utilis from a urinary tract infection. In the present case, the organism was associated with chronic, symptomatic disease. The significance of this unusual, low-virulence isolate from a case of urinary tract infection is discussed.

The incidence of yeast infections has increased during the past 2 decades (4, 8, 13, 19). Accompanying the increase is an expansion in the species recognized to cause disease (5, 8). Some of the species are new, previously undescribed species, such as Candida dubliniensis, while others are well-established industrial or environmental species, e.g., Candida lipolytica. In many cases, the newly recognized species are associated with fungemia, infected catheters, or onychomycosis (1, 8, 20).

The most common yeasts causing complicated and uncomplicated urinary tract infections (UTIs) are Candida albicans and Candida glabrata (10, 11). Systemic disease caused by the latter organism is usually associated with patients who are receiving fluconazole as antifungal therapy, but this species was a common etiologic agent prior to the fluconazole era (summarized in reference 18). However, the dominance of the species depends on whether the patient has been or is catheterized (10, 11). In patients who have not been exposed to a urinary catheter, Candida tropicalis and C. glabrata are the most common isolates (11). Examples of other fungal agents reported to cause UTIs include Candida kefyr, Candida guilliermondii, and Rhodotorula species (18). As some of these organisms may be members of the host’s normal microbiota, the detection of these organisms in urinary tract specimens, especially clean-catch or catheterized (“in-and-out”) urine samples, may sometimes be ignored by physicians. Current definitions of infectious UTI involve symptomatology (e.g., painful micturition), polymorphonuclear leukocytes in the urine, leukocyte esterase positivity, and the presence of a single uropathogen or uropathogen predominance within a culture (10, 14, 15, 24). In the absence of these defining signs, the diagnosis of UTI is not established, and consequently, the patient may not be administered any antimicrobial therapy. The presence of a urinary system obstruction confounds the diagnosis of UTI, as the obstruction may lead to higher microbial cell concentrations without concomitant greater symptomatology.

Here, we present a case of chronic UTI presumptively due to a single strain of Candida utilis over at least a 3-year period in an elderly patient. This is the first reported case of UTI due to C. utilis.

An incomplete medical history of the patient was available and is summarized in Table 1. An 88-year-old male patient presented in April 1994 to an outpatient urology clinic due to urinary retention complaints and difficulty voiding. Microbiologic analysis was not stated in the patient’s chart, but at the initial visit, the patient’s bladder was irrigated with a neomycin solution following drainage of the residual urine. A subsequent visit (interval of 5 months) revealed that the patient’s serum creatinine had risen slightly but was at the upper end of the normal range. The first microbiologic evidence of a possible infectious process was obtained in January 1995, when the drained postvoid urine was found to contain numerous leukocytes and erythrocytes. No antifungal therapy was administered at that time. During the course of the subsequent 2.5 years, repeat isolations of yeasts from drained, “infected” urine occurred. The drained urine in these instances was described as infected due to cloudiness and pyuria. A total of four specimens were found to contain the yeast, and in two instances, other organisms (bacteria) were found. However, the bacteria found on the two occasions differed. In none of these visits did the yeast concentration exceed 10^5 CFU/ml, and at no time was antifungal therapy implemented. The yeast was only identified as a “Candida species, not C. albicans.” However, during the 2.5-year period, the patient’s serum creatinine rose to 1.7 mg/dl, which is higher than the normal upper limit of 1.3 mg/dl and the patient’s prostate-specific antigen level (2.3 μg/ml) was noted in June 1995 to be at the upper end of the normal range (2.8 μg/ml). In November 1997, the patient presented to the emergency department of the University of Virginia Medical Center with multiple complaints, including nocturia (two or three episodes per night). A clean-catch urine sample revealed a single yeast-like organism on a blood agar plate (5% CO2...
35°C) at >10⁵ CFU/ml within 24 h. The patient was noted to have benign prostate hypertrophy and chronic obstructive pulmonary disease. No antifungal therapy was begun at that time. In April 1998, the patient returned to the emergency department, where an in-and-out catheterized urine sample again demonstrated yeast at >10⁵ CFU/ml. Further follow-up was not available.

None of the yeast isolates obtained in the outpatient urologic clinic were available for species identification. However, using standard yeast identification methods (26), including the germ tube assay, C. albicans screen (Carr-Scarborough), morphology on cornmeal agar, and a commercial auxanographic system (API 20C AUX; Bio-Merieux), along with subsequent additional testing with the recently introduced RapID yeast identification system (Innovative Diagnostic Systems), the organisms isolated from the specimens obtained during the emergency department visits (i.e., the isolates from November 1997 and April 1998) were identified as C. utilis (teleomorph, Pichia jadinii). This species does not produce germ tubes in the screening procedure and is therefore consistent with the isolates that were called Candida species, not C. albicans. The two isolates shared key characteristics associated with C. utilis (Table 2). The RapID profile number for the November 1997 isolate was 526023. The second isolate was not tested with the RapID system.

To confirm that the two C. utilis isolates were of the same strain, they were compared to each other and to the unrelated C. utilis ATCC 22023 isolate by karyotyping using pulsed-field gel electrophoresis (PFGE) and by restriction enzyme analysis (REA) with HindIII and EcoRI as described by Arif et al. (3) with minor modifications (Fig. 1). For PFGE, electrophoresis was performed in 1.1% agarose in Tris-borate-EDTA buffer at 12°C and 65 V. The pulse times were ramped from 840 to 640 s over 48 h and from 640 to 440 s over 24 h and finally held constant at 440 s for 24 h. DNA for REA was prepared from overnight broth cultures by spheroplasting the cells with Zy-

### TABLE 1. Medical history of index patient beginning with first visit to an outpatient urology clinic

<table>
<thead>
<tr>
<th>Date (mo, yr)</th>
<th>Microbiological result</th>
<th>Serum creatinine (normal range, [mg/dl])</th>
<th>Treatment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>April 1994</td>
<td>ND or NA</td>
<td>1.2 (0.7–1.3)</td>
<td>Neomycin instilled</td>
<td></td>
</tr>
<tr>
<td>September 1994</td>
<td>ND or NA</td>
<td>1.3 (0.7–1.3)</td>
<td>None stated</td>
<td></td>
</tr>
<tr>
<td>January 1995</td>
<td>70,000 CFU of Candida sp. not C. albicans</td>
<td>Normal creatine kinase</td>
<td>Neomycin instilled</td>
<td>Numerous leukocytes and erythrocytes in urine</td>
</tr>
<tr>
<td>June 1995</td>
<td>62,000 CFU including Klebsiella pneumoniae, Pseudomonas aeruginosa, and Candida sp. not C. albicans</td>
<td>1.5 (0.7–1.3)</td>
<td>Neomycin instilled</td>
<td>Prostate-specific antigen, 2.3 (normal high, 2.8) µg/ml; urine appears infected</td>
</tr>
<tr>
<td>October 1995</td>
<td>20,000 CFU including gram-positive cocci (&lt;20%) and Candida sp. not C. albicans</td>
<td>1.5 (0.7–1.3)</td>
<td>None stated</td>
<td>Urine does not appear grossly infected</td>
</tr>
<tr>
<td>February 1996</td>
<td>No growth</td>
<td>Not stated</td>
<td>Neomycin instilled</td>
<td>Cloudy urine</td>
</tr>
<tr>
<td>June 1996</td>
<td>Approximately 50,000 CFU of Candida sp. not C. albicans</td>
<td>Not stated</td>
<td>Neomycin instilled</td>
<td>Cloudy urine</td>
</tr>
<tr>
<td>November 1997</td>
<td>C. utilis at 10⁵ CFU/ml of clean-catch urine</td>
<td>1.7 (0.7–1.3)</td>
<td>Cardura (for BPH) started</td>
<td>BPH noted, nocturia 2–3×, high leucocyte count, chest X-ray reveals COPD</td>
</tr>
<tr>
<td>March 1998</td>
<td>In-and-out catheter urine with 10⁵ CFU of C. utilis/ml</td>
<td></td>
<td></td>
<td>Incontinence due to Cardura</td>
</tr>
<tr>
<td>April 1998</td>
<td></td>
<td></td>
<td></td>
<td>API profile same as November 1997; RapID also performed</td>
</tr>
</tbody>
</table>

* The age of the patient at the first history note was 88 years. The medical history is incomplete. However, an early note in the chart indicates that the patient had had urinary retention complaints for many years (unspecified duration).
* ND, not done.
* NA, not available.
* BPH, benign prostatic hypertrophy.
* COPD, chronic obstructive pulmonary disease.

### TABLE 2. Key microbiologic characteristics of patient isolates

<table>
<thead>
<tr>
<th>Characteristic(s)</th>
<th>Result</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>API 20C AUX profile</td>
<td>6400233 or 6400333 (questionable celllobiose assimilation)</td>
<td>No key</td>
</tr>
<tr>
<td>RapID yeast profile</td>
<td>526036</td>
<td>C. utilis (“adequate” identification)</td>
</tr>
<tr>
<td>Nitrate assimilation</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>Urease</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Cycloheximide sensitivity (500 µg/ml)</td>
<td>Sensitive</td>
<td></td>
</tr>
<tr>
<td>Morphology on cornmeal agar</td>
<td>Few pseudohyphae, elongated single conidia arising from pseudohyphae</td>
<td></td>
</tr>
<tr>
<td>Asci and ascospores on V8 juice agar</td>
<td>Absent</td>
<td>Pichia anomala is typically positive</td>
</tr>
<tr>
<td>Odor (Sabouraud dextrose agar [Emmons], 35°C, 24 h)</td>
<td>Pearlike, resembling amyl acetate; upon further incubation, it became more ethanolic</td>
<td>Similar to C. utilis type strain</td>
</tr>
<tr>
<td>Raffinose assimilation</td>
<td>Negative</td>
<td>P. anomala is positive</td>
</tr>
</tbody>
</table>
molyase 20T in 1 M sorbitol–50 mM potassium phosphate buffer (pH 7.5), collecting the cells by centrifugation, and lysing them in GES buffer (5 M guanidinium thiocyanate, 100 mM EDTA, 0.5% laurylsarcosine). DNA was isolated as described by Arif et al. (3) and stored at −20°C. Aliquots of 20 μl were digested for 4 h with 10 to 15 U of HinfI and EcoRI at 37°C, and the fragments were separated by electrophoresis in 0.8% agarose using Tris-borate-EDTA buffer at 30 V for 16 h. The DNA was visualized by staining with ethidium bromide.

The American Type Culture Collection strain was used to demonstrate that the molecular methods could distinguish strains of C. utilis. Both PFGE and REA demonstrated that the two patient isolates were indistinguishable but were easily differentiated from the ATCC 22023 isolate. PFGE demonstrated that there is karyotype variability among C. utilis isolates (25). In association with the auxanographic profiles, the molecular methods also provided greater confidence that the patient’s funguria during the 6-month period separating the two yeast isolates was due to the same strain.

Based on these results, we suggest that the patient was infected with a single strain of C. utilis for at least 6 months. Given that yeasts isolated from his urine specimens during the previous 2.5 years behaved similarly with the germ tube test, it is possible that the patient was chronically infected with C. utilis for greater than 3 years, but this possibility remains speculative. This case is not an instance of recurrent infection, as no antifungal therapy was administered and there is no evidence that the urine was mycologically sterile during the course of the patient’s history.

The patient’s infection, with its associated chronicity and unusual etiology, highlights several issues regarding the clinical assessment of UTI in elderly individuals. For example, microbiologic criteria for UTI are conventionally based on bacteriuria as originally described by Kass (12). Such criteria may be inappropriate for funguria (7, 10), particularly as the yeast cell concentration may not have any predictive value (10, 22, 23). In the elderly, the significance of a high fungal concentration is less clear, as obstructions or urinary tract damage could allow insufficient flushing or provide a nidus for organisms. Thus, the apparent asymptomatic presentation (i.e., symptoms not referable to the urinary tract [9, 14]) associated with obstruction may be a misnomer, as these patients do have symptoms, including pyuria and nocturia. Nicolle (17) noted that no long-term adverse effects have been attributed to asymptomatic bacteruria, although the condition may persist for years. However, this argument may not be true for funguria. Neumann and Rakower (16) demonstrated that there is higher associated mortality in critically ill patients with funguria (mostly due to C. albicans) than in patients with bacteruria. Whether the same is true for patients with less severe disease is not clear (7).

C. utilis is an industrially important yeast, as it is capable of several useful nonethanolic fermentation reactions that result in the production of various organics, such as acetaldehyde (21). As a pathogen, C. utilis has been reported as a rare agent of fungemia (2, 6). On culture on standard clinical mycologic media, the organism produced a distinct aroma, resembling amyl acetate or peans. Further incubation was accompanied by production of an ethanolic aroma. The determination that the isolate was the unusual yeast C. utilis and not C. albicans suggests that identification of yeast isolates from cases of fungal UTIs to the species level may provide useful clinical information. C. utilis is a low-virulence organism, yet in the present case, the organism elicited an inflammatory response (pyuria) and caused chronic infection. Thus, the presence of high concentrations of an unusual yeast or a yeast typically considered to be of low virulence during one of the first clinic visits could suggest that the patient has some underlying problem that will manifest symptoms (e.g., benign prostatic hypertrophy) sometime later. Also, given the fermentative ability of C. utilis, an intriguing speculation is that the organism’s metabolic by-products could exacerbate the underlying problem or referable problems.

REFERENCES