Candida norvegensis Peritonitis and Invasive Disease in a Patient on Continuous Ambulatory Peritoneal Dialysis

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Received 25 August 1989/Accepted 6 April 1990

We report a case of Candida norvegensis invasive disease in an immunosuppressed renal transplant patient on continuous ambulatory peritoneal dialysis. Multiple cultures of peritoneal fluid, blood, and tracheal suction done over a 2-week period were positive for this unusual isolate. Despite treatment with amphotericin B and flucytosine the patient died. This is the first report of C. norvegensis fungemia documented by culture.

Fungemia and invasive disease caused by Candida spp., particularly Candida albicans, are increasingly encountered as the use of antibacterial chemotherapy, antineoplastic cytotoxic therapy, other types of immunosuppressive therapy, and permanent indwelling plastic catheters becomes more widespread. In continuous ambulatory peritoneal dialysis (CAPD), the permanent peritoneal catheter represents a potential focus of infection, and peritonitis remains the major complication of CAPD. Peritonitis with fungal pathogens is well recognized in CAPD, is generally more complicated than bacterial peritonitis, and is often associated with an unfavorable outcome (3, 4). The occurrence in nature of Candida norvegensis is unknown, and although this yeast has been isolated from clinical specimens on rare occasions (1), to our knowledge it has not been documented as causing severe disease in humans. We report a fatal case of a patient with C. norvegensis fungemia related to CAPD peritonitis.

Case report. A 35-year-old male with end-stage renal failure received his second renal transplant 16 March 1988 after 30 months of CAPD. Postoperatively the patient received immunosuppressive therapy with prednisone, cyclosporine, and azathioprine, and peritoneal dialysis was continued. On 5 April severe upper gastrointestinal bleeding necessitated a laparotomy operation for a penetrated duodenal ulcer. The patient was given cefuroxime for 7 days after abdominal surgery. On 20 April the patient was febrile (38.5°C) and pneumonia was suspected clinically and radiologically. Cefuroxime was started but changed to intravenous vancomycin on 22 April since the peritoneal fluid grew Enterococcus faecalis on 5% horse blood agar after 24 h of incubation. In addition, peritoneal dialysis with vancomycin was started. However, renal function decreased and a change to intravenous erythromycin was considered necessary. The temperature subsequently was normalized. Because graft rejection was suspected, a renal biopsy was performed on 26 April, and immediately afterwards the patient suffered cardiovascular collapse with aspiration to the lungs. Cefuroxime, netilmicin, and metronidazole were started prophylactically, and peritoneal dialysis was continued. On 27 April blood cultures grew gram-negative bacilli (later identified as Escherichia coli) and cefuroxime was altered to cefazidime, with supplementary ceftazidime in the peritoneal dialysis fluid.

On the same day (27 April) the peritoneal fluid grew C. norvegensis and flucytosine was added to the peritoneal dialysis fluid. Hemodialysis was started in parallel because of overhydration, but the patient deteriorated, with symptoms of adult respiratory distress syndrome. From 30 April on, C. norvegensis and C. albicans were repeatedly cultured from the peritoneal fluid, while C. norvegensis was cultured from a tracheal suction. Lung radiography showed the progression of diffuse infiltrates, which initially were believed to reflect adult respiratory distress syndrome. The patient continued to be febrile despite continuous treatment with broad-spectrum antimicrobial agents; on 3 May the treatment was changed to erythromycin and sulfamethoxazole-trimethoprim, and amphotericin B was given in addition to flucytosine in the peritoneal dialysis fluid. On 5 May C. norvegensis still was recovered from the peritoneal fluid, this time together with C. albicans. On 6 May erythromycin and sulfamethoxazole-trimethoprim were stopped, since there was no clinical effect, and pneumonia with Pneumocystis carinii and Legionella spp. were ruled out. The patient was febrile, and on 10 May positive blood cultures from 4 and 6 May showed yeast cells (later identified as C. norvegensis). Intravenous treatment with amphotericin B was started, but the patient died on 11 May in respiratory failure. Necropsy was not performed.

Mycological study. (i) Morphological characteristics. C. norvegensis formed yellowish grey colonies on Sabouraud maltose agar (pH 4.0) at 25 and 37°C after 2 days and produced no filaments in the serum tube test (7). On cornmeal agar with the Dalmau technique the isolates produced pseudohyphae and blastoconidia but not chlamydoospores.

(ii) Biochemical features. Characterization of the yeast isolates was performed at the mycological laboratory of the Statens Seruminstitut. Biochemical tests were performed in liquid yeast nitrogen base (Difco Laboratories) with 0.5% concentrations of various carbon sources and read after 7 days of incubation (2). There was no fermentation of glucose. The following carbon sources were assimilated: ethanol, glycerol, salicin, lactic acid, succinic acid, and citric acid; no assimilation occurred when galactose, sorbose, sucrose, maltose, trehalose, lactose, melibiase, raffinose, melitiose, inulin, xylose, arabinose, ribose, rhamnose, erythritol, mannitol, and inositol were used as the sole carbon sources. No hydrolysis of urea and no growth on 0.05% cycloheximide occurred; nitrate was not utilized as a sole nitrogen source. Isolates were identified by the computer program developed by Barnett et al. (J. A. Barnett, R. W. Payne, and D. Yarrow, Yeast Identification PC Program for IBM PC and Compatible Computers, 1987).
(iii) **Antimycotic susceptibility.** Susceptibility tests were carried out on yeast morphology agar (pH 6.0) (Difco) and read after 48 h. The agar contained antimycotic agents solubilized in 0.1 N HCl or distilled water and further diluted in the agar to concentrations ranging from 25 to 0.1 μg/ml as twofold dilutions. Each 9-cm plate was inoculated with 50 μl of a yeast suspension, with approximately 10^5 CFU/ml spread over the surface. The MICs for the initial C. norvegensis isolate were 0.2 μg/ml for amphotericin B, 3.2 μg/ml for flucytosine, and 0.4 μg/ml for ketoconazole. The MICs for an isolate from 7 May (after 10 days of flucytosine and 4 days of amphotericin B therapy) increased to 0.8 μg/ml for amphotericin B, 12.5 μg/ml for flucytosine, and 1.0 μg/ml for ketoconazole.

The patient described here had several risk factors for a systemic fungal infection: immunosuppressive therapy, abdominal surgery, ongoing antibacterial chemotherapy, and permanent indwelling plastic catheters. The portal of entry for fungemia was most likely the peritoneal cavity, since C. norvegensis was isolated from the peritoneal fluid 1 week before the blood isolation. Moreover, it is known that the intraperitoneal cellular and humoral mechanisms of defense are inadequate for protection against Candida spp. in CAPD patients (5), a fact which is reflected by the appearance of fungal peritonitis in such patients (3, 4). Whether the primary focus was infection of a peritoneal catheter or a consequence of gastrointestinal surgery cannot be definitely answered. The patient was also infected by C. norvegensis in the lower airways during mechanical ventilation, but this could have been caused by aspiration of the gastrointestinal contents. C. norvegensis was cultured together with C. albicans from the peritoneal fluid three times, but only C. norvegensis proved to be invasive, as demonstrated by blood cultures. Whether the clinical course could have been altered by prompt removal of the peritoneal catheters when the diagnosis of fungal peritonitis was established remains unknown.

There does not appear to be a consensus on the best therapy for CAPD patients with fungal peritonitis. Many authors have recommended immediate removal of the catheter, whereas others have suggested a more flexible approach (3) which may permit antifungal therapy to be given before a decision about the removal of the catheter is made. The method used for antimycotic susceptibility testing has been in use for more than 15 years in our laboratory, and of 1,393 Candida isolates received for susceptibility testing, there were 1,159 (83%) for which the MIC of amphotericin B was ≤0.2 μg/ml (unpublished data). Furthermore, the MICs for the initial C. norvegensis isolate did not differ from those reported by others (6) for Candida clinical isolates. The occurrence of a higher MIC during therapy is in agreement with a previous report of resistance of C. norvegensis to flucytosine (1).

**LITERATURE CITED**