Disseminated Geotrichum candidum Infection

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The pathogenicity of the fungus Geotrichum candidum in humans has not been clearly defined. A patient with acute leukemia who developed a fatal disseminated G. candidum infection while neutropenic is described. At autopsy examination, this patient was misdiagnosed on the basis of histopathology as having disseminated candidiasis until G. candidum was isolated from postmortem culture specimens. The emergence of this organism as an occasional pathogen in leukemic patients is of interest and illustrates the importance of obtaining fungal cultures. There is a need for more effective drugs for antifungal prophylaxis and therapy.

Geotrichum candidum is a ubiquitous fungus which is rarely pathogenic in humans. Only one case of disseminated infection has been described previously, and its significance has been questioned (4, 8). We describe one patient with acute leukemia who had a disseminated infection caused by G. candidum, thus demonstrating its potential virulence in this patient population. Some aspects of pathogenesis, diagnosis, and treatment are also discussed.

Blood specimens were inoculated in tryptic soy broth and processed by a radiometric blood culture system (BACTEC; Johnston Laboratories, Inc., Towson, Md.). After initial isolation, the fungus was transferred to the mycology laboratory for further workup. Specimens from other sites (urine, sputum, catheter site, etc.) were inoculated onto Sabouraud dextrose agar and incubated at room temperature and at 37°C. Sabouraud dextrose agar containing cycloheximide and chloramphenicol (Mycosel; BBL Microbiology Systems, Cockeysville, Md.) was incubated at room temperature, while brain heart infusion with 5% sheep blood was incubated at 37°C. Tissue obtained from autopsy material was cut into small pieces and sent to the mycology laboratory for fungal isolation by the above-described methods of culturing. Fungal identification was based on morphological and biochemical characterization by both the API 20C system (Analytab Products, Plainview, N.Y.) and the Uni-Yeast Teks system (Flow Laboratories, Inc., McLean, Va.). G. candidum was identified by the presence of true hyphae and arthroconidia and the absence of bactoconidia. Particular features of G. candidum which helped to differentiate it from Trichosporon spp. included the following: absence of urea utilization and lack of assimilation of maltose, sucrose, lactose, cellobiose, inositol, raffinose, and trehalose. All of these reactions were tested by the combination of the API 20C and Uni-Yeast Tek systems.

Pieces of biopsy tissue were fixed in 10% buffered Formalin and embedded in paraffin. Tissue sections (5 to 6 μm thick) were stained with hematoxylin and eosin, periodic acid-Schiff stain, and Gomori methenamine-silver stain.

A 47-year-old female was diagnosed as having chronic myelogenous leukemia in 1973. The benign phase of the disease was controlled with hydroxyurea until 1978, when she developed lymphoid blastic transformation and was treated with vincristine and prednisone without response. She was admitted for further therapy with rubidazone, at which time the physical examination was unremarkable. Blood and bone marrow studies documented the persistence of a blastic crisis.

Her neutrophil count fell to <100/mm³ of blood and remained at this level throughout her entire course. On day 17 following chemotherapy, she became febrile and was given ticarcillin and trimethoprim-sulfamethoxazole. G. candidum was isolated from four blood cultures and two urine cultures collected on day 17. Numerous colonies were found in all these culture specimens, and G. candidum was isolated from Sabouraud dextrose agar incubated at room temperature and at 37°C. G. candidum was also isolated from culture specimens collected from the site of a central venous catheter. Intravenous amphotericin B and leukocyte transfusions were added to the antimicrobial regimen 2 days later when this information became known. On day 20, a 1-cm nodular erythematous skin lesion was noted on the upper right arm. Biopsy of the skin lesion was noted on the upper right arm. Biopsy of the skin lesion showed irregularly septated hyphae, and G. candidum was cultured from the specimen. The patient subsequently developed extensive bilateral bronchopneumonia and progressive hepatic and renal failure. She died on day 26 of chemotherapy after a total dose of 90 mg of amphotericin B. Histopathological findings at autopsy revealed a disseminated fungal infection. The hyphal elements were elongated, were infrequently and irregularly branched, and varied in diameter and length. However, budding yeasts were also seen. G. candidum was cultured from multiple sites. No other organism was cultured from any of these sites. Infection involved the heart, lungs, liver, spleen, peripancreatic soft tissue, hilar and retroperitoneal lymph nodes, and the bone marrow. Both kidneys contained 1- to 2-mm nodules scattered throughout the parenchyma. Microscopic examination of these nodules revealed fungal abscesses that only yielded G. candidum in cultures. There was no evidence of residual leukemia.

G. candidum is a fungus that belongs to the class Fungi Imperfecti. It is commonly found in nature and is part of the normal flora of human skin and gastrointestinal tract. Its role as a human pathogen is not clear, although it has been associated with bronchopulmonary, oral, cutaneous, and gastrointestinal pathology (8). Only one patient with a disseminated infection caused by G. candidum has been described previously. The significance of this particular case was questioned, however, and culture documentation of

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widespread \textit{G. candidum} infection was not presented (4, 8). Evidence for dissemination in six other reported cases is lacking (1, 5, 7, 10, 11). All six patients had self-limited fungemia. In four of these six patients who died, death could not be attributed to geotrichosis, and tissue invasion was not present at autopsy. In contrast, our patient was diagnosed premortem and had documented disseminated disease. Embolic skin lesions are known to occur with other fungi but have not been previously described with \textit{G. candidum}. Biopsy and culturing of these skin lesions, as are done in our patients, can be helpful for early diagnosis and possible therapeutic interventions against disseminated geotrichosis. Fungal stains show septate hyphae in infrequent and irregular branching. The presence of budding yeasts in this case suggests that an invasive coinfection caused by \textit{Candida} or \textit{Trichosporon} sp. could have been present but was overgrown on the cultures by \textit{G. candidum}. At times, hyphae may be indistinguishable from those caused by other fungi, including \textit{Candida} sp., \textit{Trichosporon} sp., and \textit{Aspergillus} sp. (6). The preliminary histopathological diagnosis at autopsy was that of disseminated candidiasis. This diagnosis was revised, however, in the light of the multiple positive cultures for \textit{G. candidum} and the absence of growth of any other organism, in particular, \textit{Candida} sp., \textit{Trichosporon} sp., or \textit{Aspergillus} sp. In addition, the acute branching of some of the hyphal elements argued against the diagnosis of candidiasis. Because of these morphological similarities, identification of the fungus obtained from cultures is required to diagnose Geotrichum infections.

The therapy and outcome of Geotrichum infections are dependent on the degree of invasion of the organism and the status of the host. Ghamande et al recommended no therapy with amphotericin B in view of the usual benign course of geotrichosis (5). Sheehy et al. suggested that Geotrichum spp. are not very virulent and lack the ability to colonize renal tubules. This suggestion was based on the rarity of disseminated disease, the paucity of tissue invasion in most reported cases, the absence of renal invasion in previous reports, and the rapid clearance of the fungus in the patient they described (10). Our study demonstrates that Geotrichum spp. can cause virulent and fatal infections in humans. The presence of multiple kidney abscesses in our patient reveals the capacity of the organism for renal tissue invasion, which may result in kidney failure. It should be kept in mind, however, that in and of themselves, urine cultures positive for Geotrichum spp. do not indicate kidney infection. Even in the presence of high numbers of polymorphonuclear leukocytes, the virulence of the organism should be questioned.

The efficacy of amphotericin B in \textit{G. candidum} infections is difficult to assess in view of the small number of patients treated. The presence of severe granulocytopenia in our patient probably contributed to her fatal outcome (3). Another determining factor could be whether the organism is susceptible to the antifungal agent administered. Data concerning such in vitro susceptibility are scanty. The organism seems to be susceptible, however, to amphotericin B and miconazole (2, 9).

Although rare, \textit{G. candidum} is a potential pathogen in immunocompromised hosts. Its incidence may be underreported, since it can be misdiagnosed histopathologically as \textit{Candida} sp., \textit{Aspergillus} sp., or \textit{Trichosporon} sp. This possibility for misdiagnosis illustrates the importance of obtaining fungal cultures in addition to histopathological data. Better awareness of its pathogenicity could delineate its true incidence, patterns of clinical disease, and responsiveness to therapy.

LITERATURE CITED