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Cerebral Phaeohyphomycosis Caused by *Chaetomium globosum* in a Renal Transplant Recipient

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A 32-year-old male patient developed headaches, vomiting, blurring of vision, and focal seizures of the left side of the face 2 months after a renal transplant. He developed a brain abscess and died. Direct KOH examination of the brain tissue demonstrated hyaline as well as dematiaceous, septate hyphae. Histologic examination of brain sections revealed polymorphous fungal elements consisting of septate, dark-pigmented hyphae, intercalary and terminal swollen fungal cells, and budding yeastlike cells characteristic of phaeohyphomycosis. *Chaetomium globosum* was isolated from the brain tissue on all of the fungal media used. This case represents the first histologically and culturally documented phaeohyphomycotic brain infection caused by *C. globosum*.

In renal transplant recipients, opportunistic fungal infections are not uncommon. Most infections are caused by such yeasts as *Candida albicans* and *Cryptococcus neoformans* (5) or mould species of the genus *Aspergillus* (12, 23, 27) and dematiaceous fungi such as *Exophiala jeanselmei* (12) and *Phialophora parasitica* (1, 18, 28). Although species of the genus *Chaetomium* are known to produce toxic metabolites on dead organic substrates (10), their isolation from clinical specimens is generally considered to reflect contamination by airborne fungi.

Only a few reports have been published implicating *Chaetomium* spp. as opportunistic pathogens causing human infections. Rippon (25) mentioned three cases of infection of dystrophic nails caused by *Chaetomium globosum*. The second species, namely, *C. funicolum*, was cultured several times for fistulous nodules in the region of the perineum and lower abdomen of a 71-year-old man who sustained a superficial injury some 4 years previously (17). Hoppin et al. (13) repeatedly isolated *C. cochliodes* from the pleural fluid of a patient with acute lymphocytic leukemia who had developed empyema, probably due to a contaminated Hickman catheter, which probably contributed to the patient's death. In 1978, Huppert et al. (14) studied a histologic preparation from brain tissue that showed microabscesses containing hyphal elements. Earlier, a *Chaetomium* sp. had been cultured from a blood clot of the patient, but no attempt was made to isolate the fungus from the brain tissue. Huppert et al. therefore considered their isolate from the blood clot to be a contaminant rather than an etiologic agent.

We present here the first documented fatal infection of the brain caused by *C. globosum* Kunze ex Fries in a renal allograft recipient.

CASE REPORT

A 32-year-old man with diabetic nephropathy had a left nephrectomy done in December 1986 in Bangladesh for uncontrolled bleeding after renal biopsy. He was referred to the Christian Medical College and Hospital, Vellore, India, where he received a renal transplant from a live relative donor in January 1987. Medication included azathiaprine, cyclosporin, and prednisolone. Two months postoperatively, he was readmitted with sudden onset of headache, vomiting, blurring vision, difficulty in walking, and focal seizures of the left side of the face. He developed left hemiparesis, right supranuclear seventh nerve palsy, and coma. Cardiovascular and respiratory systems were normal. A computerized tomography scan (26) showed evidence of right parietotemporal lobe infarction, suspected to be around a space-occupying lesion. The patient was treated for cerebral edema, and physiotherapy was initiated.

By day 14, he developed fever, bilateral pyramidal signs, and papilledema. At that time, blood and cerebrospinal fluid cultures were negative for aerobic, anaerobic, mycobacterial, and fungal organisms. Two weeks later, a second computerized tomography scan showed definite evidence of a space-occupying lesion in the right parietotemporal region. On day 32 after admission, a brain biopsy was done. The cortex looked normal, but a hard mass was found beneath it. Histopathologic examination of the biopsy specimen showed perivascular inflammation and gliosis. Nine days later, he developed transtentorial herniation and died.

MATERIALS AND METHODS

Materials. Portions of brain tissue collected at biopsy and autopsy were fixed in 10% neutral buffered Formalin for histopathologic examination. Another portion of the autopsy brain specimen was sent to the Department of Microbiology for bacterial and fungal cultures.

Histopathology. Pieces of brain tissue were fixed in 10% neutral buffered Formalin, embedded in paraffin, sectioned at 5 μm, and stained with hematoxylin and eosin (H&E), periodic acid-Schiff, Gomori methenamine silver (GMS), and GMS and H&E combination procedures for fungi (6).

Cultures. Purulent and necrotic brain tissue collected at autopsy was examined in 10% KOH by direct microscopy. It was also cultured on two sets of petri plates containing Sabouraud dextrose agar with or without antibiotics (chloramphenicol, 0.05 g/ml; cycloheximide, 0.5 mg/ml), brain

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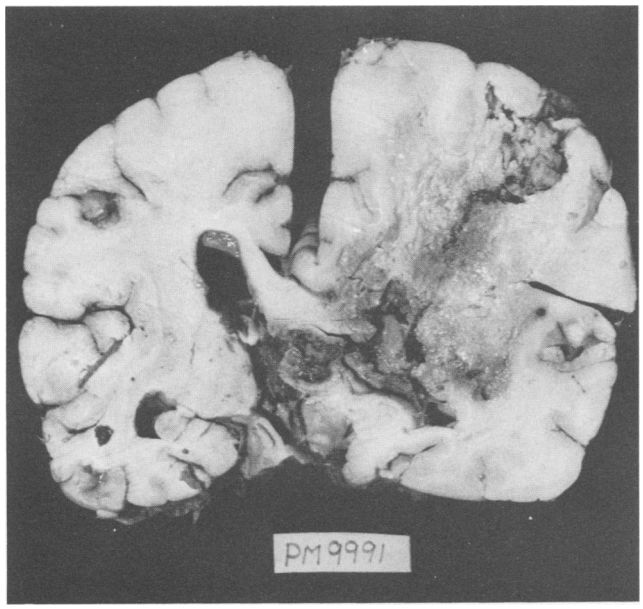

FIG. 1. Coronal section of the brain showing a large ragged abscess in the swollen right cerebral hemisphere caused by *C. globosum* CDC B-4561.

heart infusion agar, beef infusion blood agar, thioglycolate broth, and Lowenstein-Jensen medium. The culture plates, tubes, and broth cultures were incubated at 25 and 37°C. One brain heart infusion agar plate was incubated under anaerobic conditions.

Slide cultures of the isolate were prepared on potato dextrose agar and corn meal dextrose agar (Difco Laboratories, Detroit, Mich.) to study microscopic morphology. The slide cultures were incubated in the dark at 25°C for 2 weeks. The resultant growth on both the cover slip and the slide was mounted in lactophenol cotton blue, and the preparations were examined with a Zeiss universal research microscope equipped with bright-field, phase-contrast, and differential-interference-contrast optics at the Division of Mycotic Diseases, Center for Infectious Diseases, Centers for Disease Control, Atlanta, Ga.

RESULTS

Autopsy findings. Macroscopically, no significant lesion was noted in the meninges. In the brain, evidence of subfalcine and uncal herniation was found. The right cerebral hemisphere showed bulging and swelling. Coronal sections showed a large, ragged cavity abscess with surrounding areas of suppuration, edema, and softening that involved much of the white matter of the right parietal lobe and continued supralaterally with the surface surgical defect. Inferomedially, it involved the corpus callosum, lateral ventricle, caudate nucleus, internal capsule, putamen, globus pallidus, and insula and extended to the basal pedunculi. Midline structures were pushed to the left side (Fig. 1).

Histopathologic findings. Histopathologic examination of the brain biopsy specimen showed perivascular inflammation and gliosis; however, fungal elements were not detected. H&E-stained sections of brain tissues collected at autopsy revealed many discrete and confluent microabscesses surrounded by epithelioid histiocytes, huge multinucleated giant cells, and fibroblasts (Fig. 2). In other areas, there was a dispersed granulomatous inflammatory reaction composed of multinucleated giant cells embedded in a fibrovascular stroma (Fig. 3). Many of the abscesses and contiguous giant cells contained abundant fungal elements, some of which were lightly pigmented (Fig. 4). Sections stained with GMS, periodic acid-Schiff, and GMS-H&E procedures revealed that the polymorphous fungal elements consisted of branched, closely septate hyphae 4 to 6 μm wide that sometimes contained intercalary or terminal thick-walled, chlamydoconidiumlike cells up to 20 μm in diameter, budding cells, and single cells with septations in one plane (Fig. 5)—morphologic features characteristic of phaeohyphomycosis. In addition to intact fungal elements, many giant cells contained amorphous, GMS-positive granular material that represented the residuum of fungal cell wall degradation (Fig. 2). The distribution and actual number of fungal elements were much more evident when the GMS stain with H&E counterstain was used.

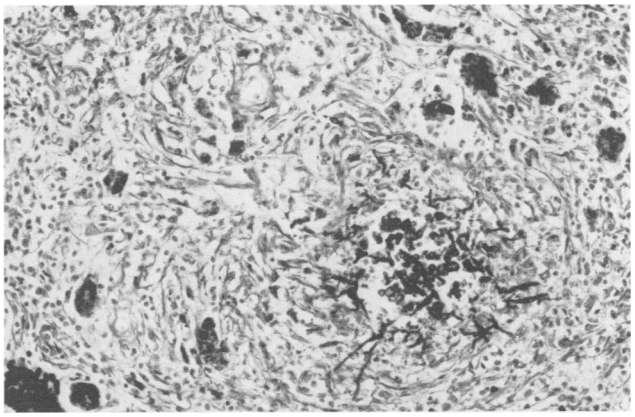

FIG. 2. Cerebral phaeohyphomycosis caused by *C. globosum*. A microabscess (lower right) contains polymorphous fungal elements and is surrounded by compact fibroblasts, epithelioid histiocytes, and multinucleated giant cells. GMS-H&E stain; magnification, ×225.

Direct microscopic examination of the brain tissue in KOH showed hyaline to lightly pigmented, septate hyphae

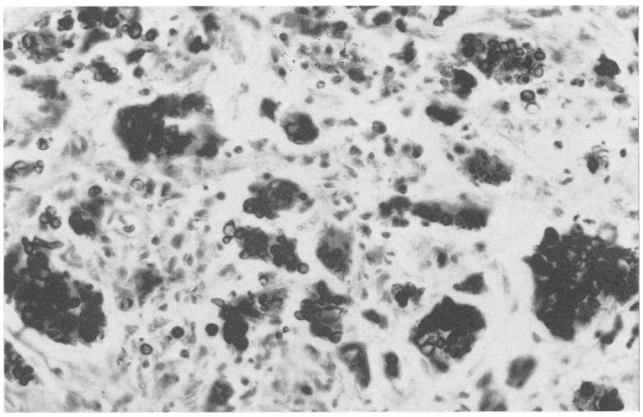

FIG. 3. Dispersed granulomatous inflammatory reaction composed of huge multinucleated giant cells embedded in a fibrovascular stroma. The giant cells contain intact fungal elements of *C. globosum* and GMS-positive granular material that represents the residuum of fungal cell wall degradation. GMS-H&E stain; magnification, ×360.

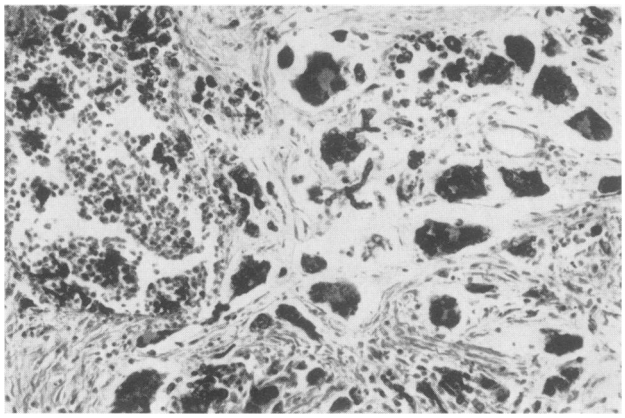

FIG. 4. Polymorphous elements of *C. globosum* within cerebral abscess (left). Giant cells at the margin of the abscess contain yeastlike cells, chains of cells, and short septate hyphae. GMS-H&E stain, magnification, ×225.

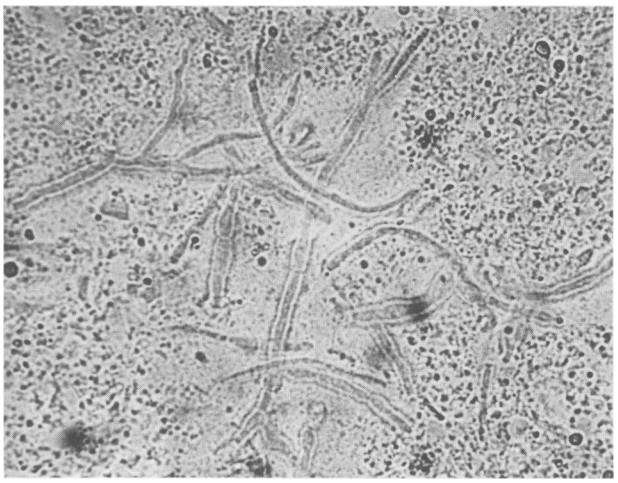

FIG. 6. Pale brown, septate hyphae of *C. globosum* in a KOH preparation of brain tissue. Magnification, ×620.

(Fig. 6). Creamy white to yellowish white, wooly colonies (8 to 10 per plate) were visible after 3 days at 25 and 37°C on all of the inoculated plates. Ten-day-old colonies became grayish as they developed black ascocarps. Microscopic examination of the ascocarps showed numerous olive-brown to black perithecia covered with long, hairlike, dematiaceous setae. Mature perithecia were ostiolate and liberated many ovate to lemon-shaped ascospores. The isolate was identified as *Chaetomium* sp. A subculture was sent to the Division of Mycotic Diseases for specific identification.

Slide cultures of the *Chaetomium* sp. (CDC 87-037597) on potato dextrose agar and corn meal dextrose agar after 2 weeks at 25°C showed numerous dark-brown to black perithecia that varied in shape from globose, subglobose to ovate with long, brown-to-black, hairlike setae. The perithecia were ostiolate and measured 200 to 300 by 200 to 280 μm. Terminal hairs were bushy, compact, undulate, and simple and spread and dropped with age. They were minutely roughened and measured 3 to 3.5 μm in diameter at their bases. The hairs were septate and tapered to paler to hyaline tops which became wavy, undulated, or kinked. The eight-spored asci were evanescent and easily extruded their spores through the ostioles of the mature perithecia (Fig. 7). The ascospores contained refractile globules and were olivaceous brown. They were broadly ovate to lemon shaped with apiculate ends and measured 9 to 12 by 6 to 9 μm. On the basis of the Ames (3) classification key, the isolate (88-037597) was identified as *C. globosum* Kunze ex Fries.

The maximum temperature of growth of the isolate was 41°C. At that temperature, growth was mycelial without any perithecial formation. A subculture of the isolate was sent to S. C. Jong, American Type Culture Collection, Rockville, Md., who confirmed its identification as *C. globosum*. It is deposited in the Division of Mycotic Diseases culture collection under accession number CDC B-4561 and in the American Type Culture Collection as ATCC 64497.

DISCUSSION

In his monograph of the family *Chaetomiaceae*, Ames (3) classified 88 known species of the genus *Chaetomium*. On

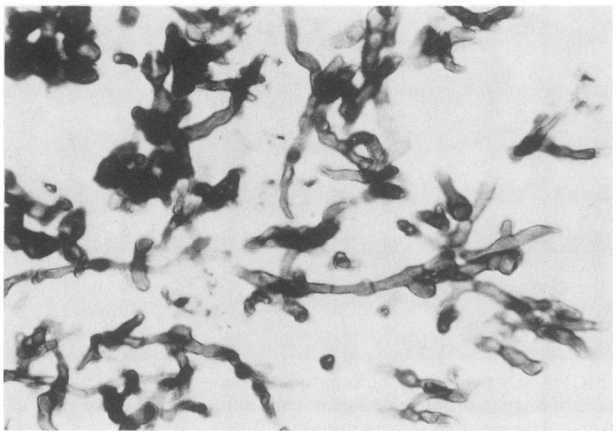

FIG. 5. Septate, branched hyphae and swollen, chlamydoconidiumlike cells of *C. globosum* in the brain tissue section. GMS stain; magnification, ×875.

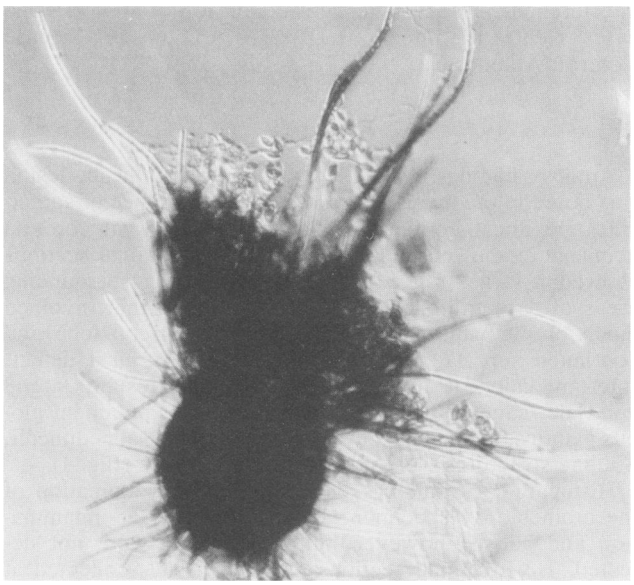

FIG. 7. Ostiolate perithecium of *C. globosum* CDC B-4561 covered with simple, long, undulate setae and extruding ascospores. Magnification, ×700.

the basis of the conspicuous characteristics of the hairs and the shapes and sizes of the perithecia, asci, and ascospores, he classified the 88 species into eight groups. The Indian isolate was classifiable under Ames group VIII, which contains 11 species that produce perithecia with terminal hairs that are unbranched, undulate, and simple. Further classification of the species is based on the shapes and sizes of perithecia, asci, and ascospores.

Human brain abscesses due to fungi (2, 5, 7, 15, 16) have been caused by *Aspergillus* spp. (2, 5, 8, 12, 23, 27, *Candida* spp. (5), *Cryptococcus neoformans* (5), various zygomycetes (22), and such dematiaceous pathogens as *Xylohypha bantiana* (4, 9, 19, 20, 24) and, more rarely, *Bipolaris hawaiiensis* (11, 21). The present case of a phaeohyphomycotic brain abscess in an immunocompromised renal transplant recipient represents the first documented systemic infection caused by *C. globosum*. In the systemic infection due to *C. cochliodes* in a patient with lymphocytic leukemia (13), the researchers speculated that the fungus had gained entry through an indwelling catheter. In the present case, our patient did not have that risk factor, and it was not clear how *C. globosum* reached the brain. In an attempt to detect the primary focus of infection, the lungs, intestines, and kidneys of the deceased were examined at autopsy. None of the organs, however, showed any evidence of fungal infection.

The initial diagnosis of a brain abscess was based on clinical symptoms and the computerized tomography scan. The deep-seated abscess probably had not been reached during the initial brain biopsy, which showed only perivascular inflammation and gliosis. Thus, a fungal etiology was not considered in the initial differential diagnosis. The postmortem findings, however, confirmed that the infection was due to *C. globosum* and that the histopathologic findings were similar to those reported for other agents of cerebral phaeohyphomycosis (4, 6, 9, 20, 24). The ability of *C. globosum* to grow at temperatures as high as 41°C indicates its potential to be a neurotropic pathogen.

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