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Disseminated Infection by *Fusarium moniliforme* During Treatment for Malignant Lymphoma

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Disseminated infection caused by *Fusarium moniliforme* is described in a 32-year-old granulocytopenic man with malignant lymphoma being treated with cytotoxic drugs and corticosteroids. Infected skin denuded by antecedent severe varicella-zoster infection was the probable source of fungemia. *F. moniliforme* grows rapidly on common mycological media as a lavender- to violet-colored mold at 25 to 37°C. Its aerial hyphae produce fusoid macroconidia and characteristic fusiform microconidia in chains. The morphology of hyphae in tissue closely resembles species of *Aspergillus* and is not diagnostically specific. Morphological characteristics which distinguish cultures of *F. moniliforme* from other medically important species of *Fusarium* are discussed.

With increasing use of cytotoxic and immunosuppressive drugs in patients with cancer or organ transplants, diagnostic microbiology laboratories are often confronted with problems in the identification of opportunistically pathogenic, frequently exotic fungi. Among these are species of the genus *Fusarium*, which belong to the class *Deuteromycetes* (*Fungi Imperfecti*), order *Moniliales*. *Fusarium* species are important plant pathogens. Although long recognized as causes of keratomycosis and superficial burn wound infections, they have been recovered only rarely from deep tissues. In the present communication we report systemic infection by *Fusarium moniliforme*, which has not previously been reported as a cause of disseminated infection. The mycological characteristics distinguishing this organism from other species of *Fusarium* and related fungi are described.

MATERIALS AND METHODS

Case report. A 32-year-old man with a 5-year history of stage IV B malignant lymphoma, diffuse mixed lymphocytic-histiocytic type, was admitted to the hospital because of widespread cutaneous varicella-zoster infection. Recently treated with bleomycin, adriamycin, cyclophosphamide, vincristine, and prednisone, he had a leukocyte count of 500/mm^3. Physical examination disclosed a temperature of 39.5°C and vesicular skin lesions that rapidly became confluent on the face and trunk, with additional discrete lesions of the extremities and buccal mucosa. Chest roentgenograms revealed a nodular infiltrate in the upper lobe of the right lung. *Escherichia coli* and *Enterobacter* species were recovered from blood cultures, resulting in treatment with cefazolin, gentamicin, carbenicillin, and leukocyte transfusions. Because of severe fluid and protein loss from extensively denuded skin, he was managed essentially as a burn patient. Cultures of multiple skin lesions and urine obtained between hospital days 5 and 11 grew *Candida tropicalis* and a mold subsequently identified as *F. moniliforme*. Heavy growth of *F. moniliforme* was also recovered from the sputum. Serum amylase rose progressively to 621 Somogyi units on hospital day 10 in the absence of signs or symptoms of pancreatitis. The clinical course thereafter was characterized by progressive renal and respiratory failure, with diffuse alveolar infiltrates on chest roentgenograms. Massive gastrointestinal bleeding, hypothermia, and a coagulation profile indicative of disseminated intravascular coagulation ensued. On the day of death, 15 days after admission, a blood culture obtained 3 days previously yielded *F. moniliforme*.

Autopsy findings. At autopsy (A76-187) no residual lymphoma was present, and the bone marrow was aplastic. Postmortem cultures of blood and lung yielded both *F. moniliforme* and *C. tropicalis*. Nonpigmented septate hyphae, compatible with *Fusarium* species but not with *Candida*, were seen in the left ventricular myocardium, kidneys, pancreas, and lungs. Infarcts were present in the latter two organs as a result of occlusion of small- to medium-sized arteries by hyphae of *Fusarium*. Yeasts and pseudohyphae of *Candida* were even more extensively disseminated in necrotic lesions of the myocardium, pericardium, lungs, esophagus, stomach, small and large intestines, peritoneum, pancreas, kidney, bladder, lymph nodes, thyroid, and skin. Intranuclear inclusions characteristic of varicella-zoster virus infection were identified in foci of parenchymal necrosis in the lungs and in residual skin lesions, from which the virus was isolated.

Media and culture methods. Primary isolation of the fungus at 25°C was achieved by inoculation of sputum, blood, urine, and homogenized biopsy and

autopsy tissues onto brain heart infusion agar (Difco Laboratories) with or without chloramphenicol, 40 mg/liter; brain heart infusion agar with 5% sheep blood; and modified Sabouraud dextrose agar with or without cycloheximide (8). Duplicate subcultures were incubated at 25 and 37°C. Observations of cultural characteristics were made on malt extract agar (Difco).

RESULTS

The fungus grew rapidly, slightly faster at 37°C than at 25°C, on all of the media that lacked cycloheximide, which inhibited growth. Morphologically identical isolates were obtained from blood, sputum, urine, and lung tissue. Incubation for 4 days on malt extract agar at 25°C produced a floccose, pale lavender-colored colony of 4-cm diameter (Fig. 1). The colony became violet in 2 weeks. Microscopic observation revealed a small number of fusoid macroconidia typical of the genus *Fusarium* (Fig. 2) and clavate to fusiform microconidia in chains (Fig. 2), characteristic of the species *F. moniliforme*. Although limited in number, macroconidia developed in clusters from conidiophores formed as lateral branches on hyphae. Macroconidia were fusoid, with two to four septa, and with or without a sharply curved apical cell and pedicellate basal cell (Fig. 2). They measured 18 to 25 by 2 to 3 μm. Microconidia were produced in chains mostly from simple conidiophores, or rarely from conidiophores with two to three phialids, on the aerial hyphae (Fig. 2). The shape of the microconidia varied from fusiform to clavate with flattened base and occasionally with one septum. The size of the microconidia ranged from 3 to 15 by 1.5 to 3 μm.

In tissue conidia were not observed, but ghost-like outlines of hyphae could be seen in histological sections stained with hematoxylin and eosin. The hyphae were observed in foci of necrosis accompanied by a scant exudate of mononuclear inflammatory cells. The fungus stained better by the methenamine silver or periodic acid-Schiff techniques, which revealed septate hyphae generally 3 to 6 μm in diameter with dichotomous branching (Fig. 3). The branches of the hyphae tended to arise at an angle of approximately 45° and to be oriented in the same direction (Fig. 4). These characteristics are not distinctive, and closely resemble the size and branching pattern of the mycelium of species of *Aspergillus*. The fungus also resembles species of *Aspergillus* in its marked predilection for vascular invasion (Fig. 5), which in this case produced occlusion of small arteries in the lungs and pancreas with resultant infarcts.

DISCUSSION

Fusarium species are soil saprophytes and plant pathogens of world-wide distribution (4). Their most important role in human disease is

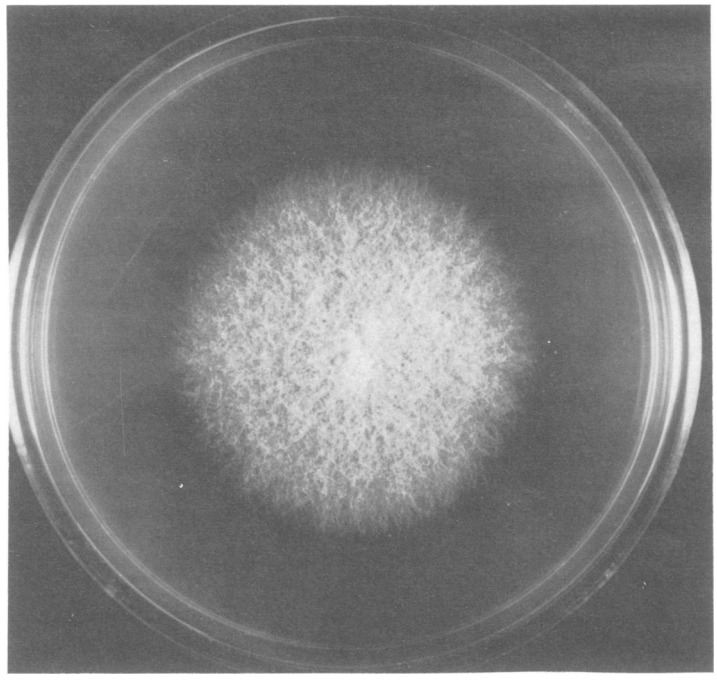

FIG. 1. *Four-day-old colony of F. moniliforme on malt agar medium.*

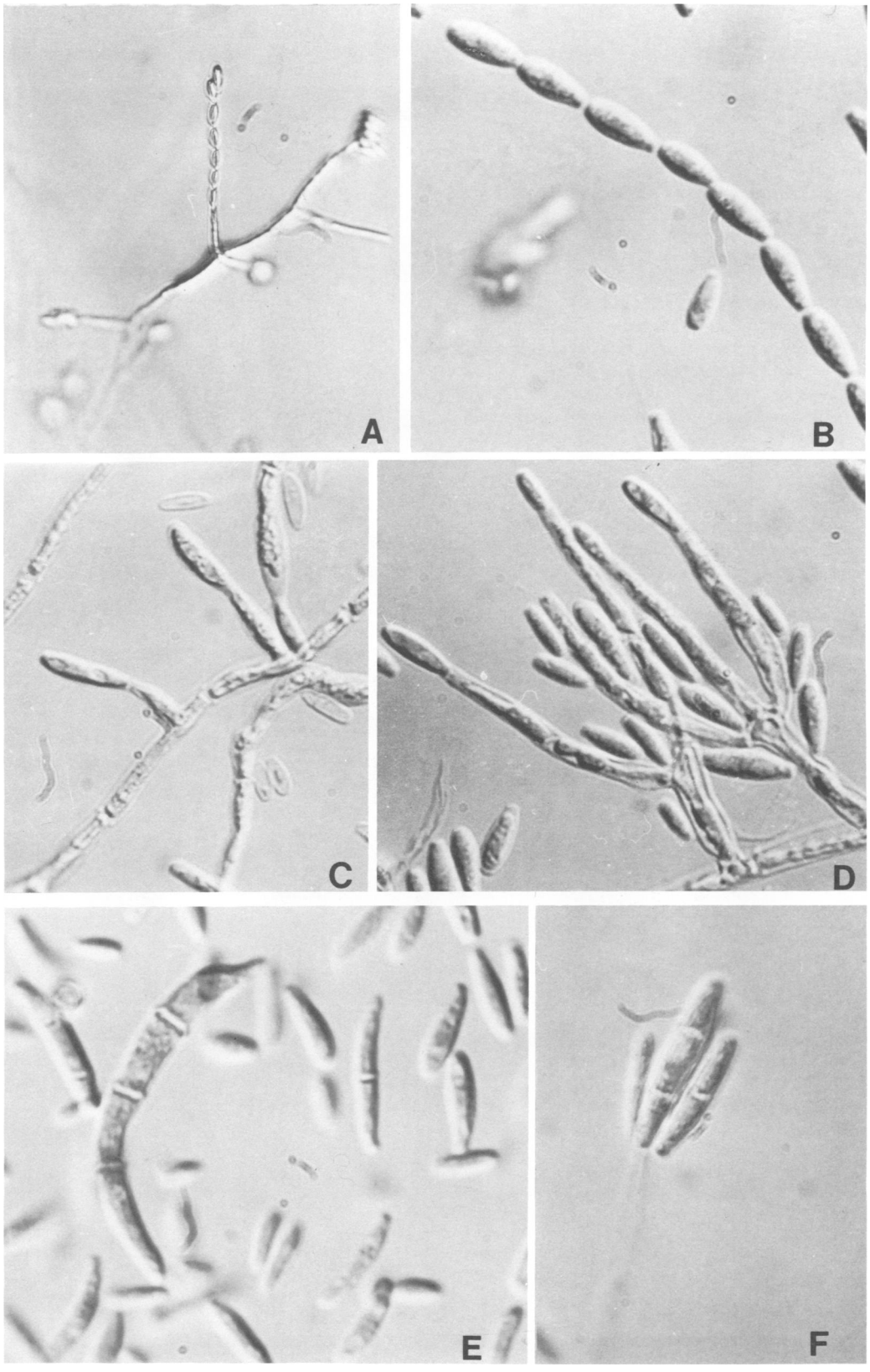

FIG. 2. *(A) Chain of microconidia produced on aerial hyphae. ×300. (B) Pyriform microconidia with flattened base. ×1,200. (C) Simple conidiophores arising from aerial hyphae. ×1,200. (D) Conidiophores with several phialids. ×1,200. (E) Macroconidia and microconidia. ×1,200. (F) Macroconidia produced in a cluster at the tip of a conidiophore. ×1,200.*

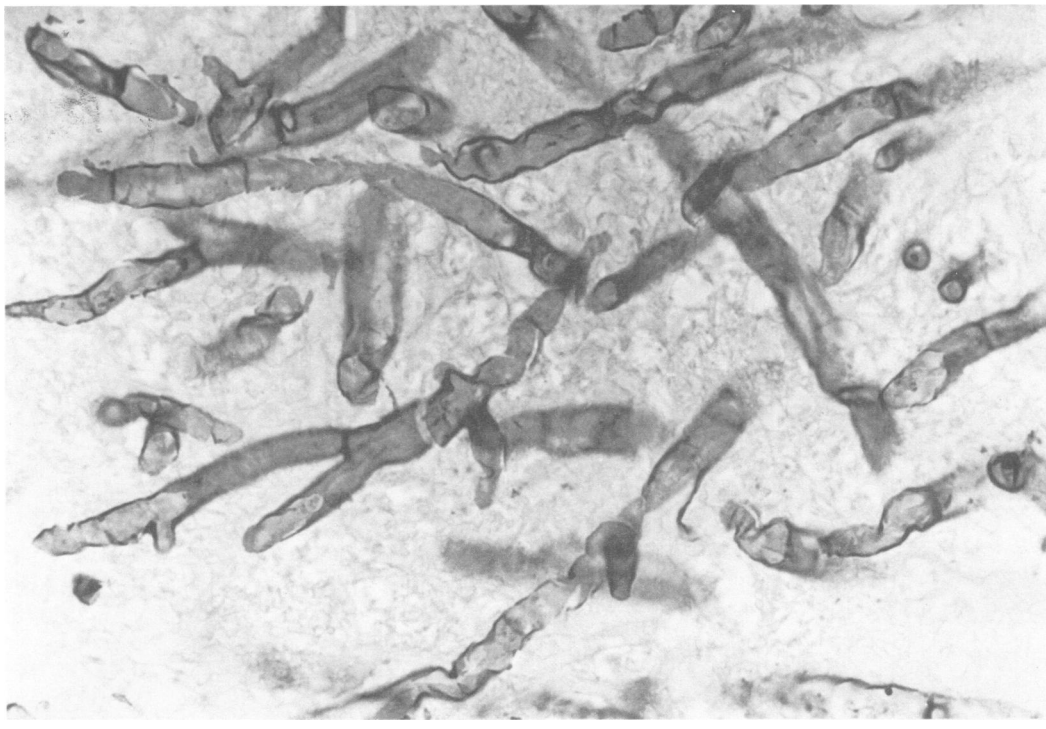

FIG. 3. *Septate hyphae of F. moniliforme. Methenamine silver stain; original magnification, ×630.*

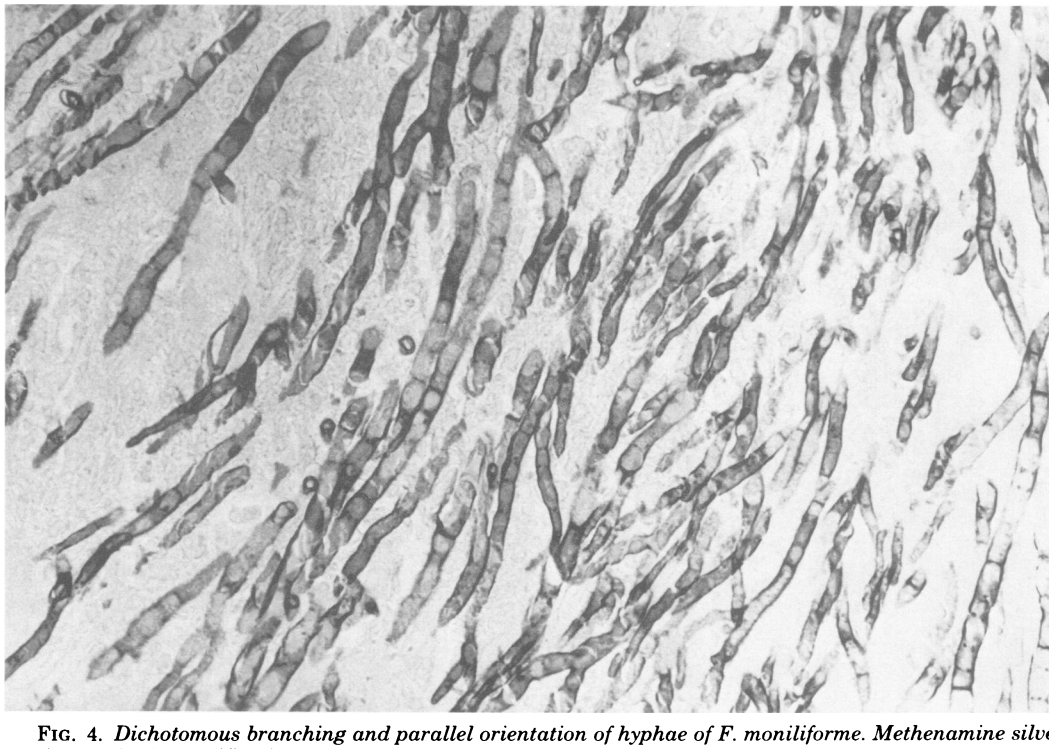

FIG. 4. *Dichotomous branching and parallel orientation of hyphae of F. moniliforme. Methenamine silver stain; original magnification, ×250.*

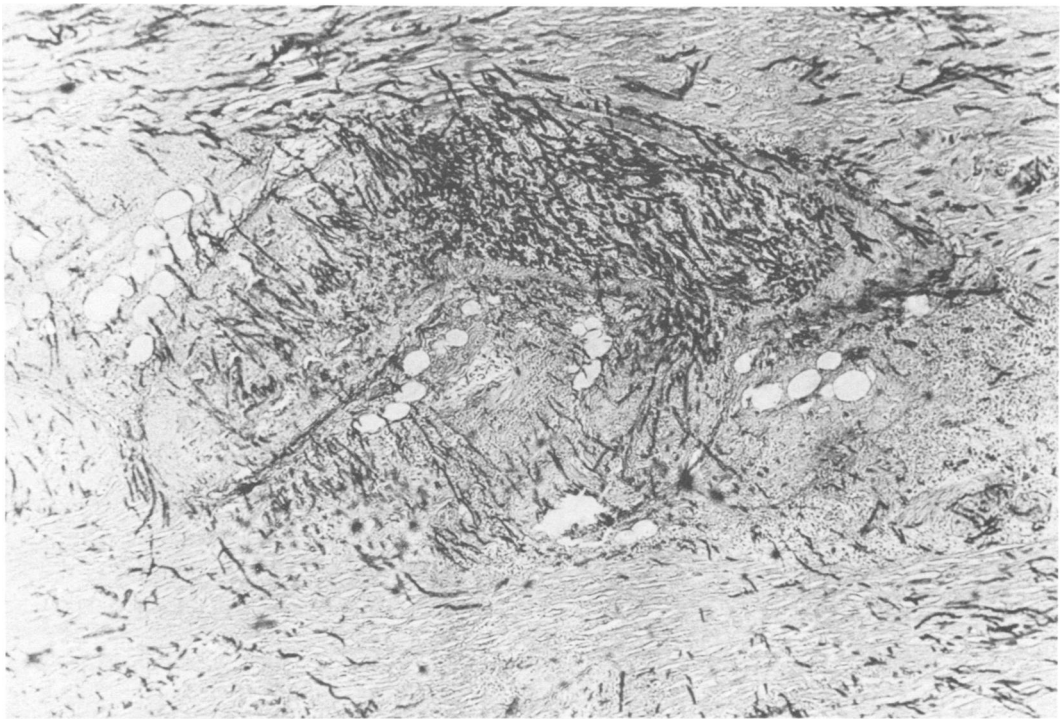

FIG. 5. *Thrombus in small blood vessel of pancreas. Hyphae are abundant in the thrombus and penetrate the vessel wall into adjacent infarcted parenchyma. Methenamine silver stain; original magnification, ×40.*

in keratomycosis. In some geographic regions such as Florida and West Africa, *Fusarium,* especially *F. solani,* is the most common agent causing this disease (10–12, 14–16, 19–23). *F. solani* and *F. oxysporum* have also colonized and sometimes infected wounds (1, 9). Infection of deep tissues is very rare. *F. oxysporum* has been isolated in pure culture from pus in a case of osteomyelitis of the tibia after a puncture wound (5). A *Fusarium* species was the cause of a facial subcutaneous granuloma in a child with probable chronic granulomatous disease (3). Disseminated infection has been caused by a *Fusarium* species in a burned child (1); by *F. solani* in a patient with acute leukemia (6); and by *F. oxysporum* in a woman with a myasthenic syndrome and aplastic anemia (13). Previous reports of *F. moniliforme* as a human pathogen are limited to two cases of corneal ulcer and one case of a pustular lesion of the hand (2, 7, 17).

The pathogenesis of infection in the present case was probably similar to burn wound sepsis. In a patient whose host defense mechanisms were severely compromised by corticosteroids and chemotherapy that resulted in granulocytopenia, confluence of extensive cutaneous lesions of varicella-zoster infection led to weeping ulcers involving more than half of the surface area of the skin. *F. moniliforme* fungemia, presumably originating from suprainfection of denuded skin, then resulted in hematogenous dissemination to the lungs, heart, pancreas, and kidneys. Infarcts in the pancreas as well as other lesions were clearly not merely agonal, because the serum amylase was elevated 9 days antemortem and rose progressively until death.

Fusarium species are readily recovered from clinical specimens. They grow rapidly as molds on a variety of solid mycological media lacking cycloheximide. In liquid media with agitation, a unicellular form has been described (17). Although easily cultured, fusaria present difficulties in identification for most diagnostic workers. The presence of fusoid macroconidia with a foot cell bearing some type of heel is accepted as the most definitive characteristic of the genus. This feature of the foot cell separates the genus from *Cylindrocarpon,* the fungus that it most closely resembles (4). Species identification of *Fusarium* is difficult because of the remarkable capacity of these fungi for rapid change in their morphology and colony color. The most distinctive feature of *F. moniliforme* is the formation of microconidia in chains. Morphological characteristics helpful in distinguishing *F. moniliforme* from the other four medically important species

TABLE 1. *Medically important species of Fusarium*

Species	Useful differential characteristics
F. moniliforme	Fusoid macroconidia; microconidia in chains
F. dimerum	Salmon-colored spore mass; micro- and macroconidia not distinct by size, conidia usually with a central septum
F. solani	None of the above; microconidiophores elongate; macroconidia widest in upper half, thick walled
F. oxysporum	Microconidiophores short; macroconidia thin walled

of *Fusarium* are listed in Table 1. A fifth fungus, *F. roseum,* has been isolated from burned skin (18). However, several *Fusarium* species formerly designated *F. roseum* are now further subclassified into additional species (4). The species status of *F. roseum* is extremely complicated and hence not included in Table 1.

Recognition of human disease caused by a *Fusarium* species rests upon identification of the fungus recovered in cultures, because the morphology of the organism in histological sections is not sufficiently distinctive to permit its differentiation from other more common pathogens, such as species of *Aspergillus* or other non-dematiaceous hyphomycetes. In the present case, the septate hyphae observed in tissue exhibit a diffuse, nonmatted pattern of growth with characteristic vascular invasion. Because these features are morphologically consistent with *Fusarium,* which was cultured from autopsy tissues although *Aspergillus* species were not, it is probable that the observed hyphae were those of *Fusarium.* Other nonpigmented filamentous fungi recognized as pathogens which might potentially be confused in tissue sections with *Fusarium* include *Petriellidium boydii* and species of *Cephalosporium.* However, *P. boydii* typically exhibits matted, dense growth of hyphae, which, moreover, usually have bulbous ends or expanded terminal cells and are not uniform in size like *Fusarium* (8). Likewise, in cases of *Cephalosporium* infection thus far reported, there have been granules or microcolonies in tissue (8) in contrast to the diffuse growth pattern of *Fusarium* or aspergilli.

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C. Booth, Commonwealth Mycological Institute, Kew, Surrey, England, confirmed our isolate as *F. moniliforme.*

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