Fusarium proliferatum as an Agent of Disseminated Infection in an Immunosuppressed Patient

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Fusarium proliferatum was reported as the agent of a fatal disseminated infection in a child with lymphoblastic leukemia. The fungus has not been reported previously to cause disease in humans, but it is closely related to the known opportunistic pathogen *F. verticillioides*. It was distinguished by the production of clavate microconidia in chains from proliferating phialides. Resistance to amphotericin B and flucytosine in vitro was shown.

Members of the genus *Fusarium* represent a group of common saprobic, phytopathogenic, and entomopathogenic members of the class *Hyphomycetes* with teleomorphs in the order *Nectriales* (12). In recent years, they have been reported with increasing frequency to cause opportunistic infections in humans (4, 43, 44). Infections reported include keratitis (4, 43), endophthalmitis (15, 30, 45), septic arthritis (23, 38), osteomyelitis (8, 37), and brain abscess (47), plus sundry other subcutaneous (2, 3, 6, 11, 51, 52), cutaneous (10, 43), and disseminated (1, 7, 22, 25, 31, 36, 40, 50, 53) infections. Several individual *Fusarium* species have been implicated in causing these infections, including *F. chlamydosporum* Woll. & Rein. (26), *F. coeruleum* (Lib.) ex Sacc. (48), *F. oxysporum* Schlecht. (3, 8, 22, 45, 50-52), *F. verticillioides* (Sacc.) Nirenb. (*F. moniliforme* Sheldon sensu stricto) (2, 10, 24, 39, 53), *F. sacchari* (Butler) W. Gams (54), *F. dimerum* Penzig (20, 55), and *F. solani* (Mart.) Sacc. (9, 15, 23, 43). Additionally, *F. anthropophilum* (A. Braun) Woll. has recently been isolated along with *F. solani* from a proven disseminated *Fusarium* infection; the degree to which each of the two species contributed to the infection could not be established (36).

In the present study we were concerned with a disseminated human infection caused by a *Fusarium* species not previously reported as an opportunistic pathogen: *F. proliferatum* (Matsushima) Nirenberg (*F. moniliforme* var. *intermedium* Neish et Leggett). This species is classified along with the known opportunistic pathogens *F. verticillioides* and *F. sacchari* in the section *Liseola* (35). It is the third species within the section *Liseola* reported to cause infections in humans.

A full clinical report regarding this case and a review of similar cases is in preparation (S. E. Richardson, R. M. Bannatyne, J. Milliken, R. Gold, and S. S. Weitzman, submitted for publication). In the present study we were primarily concerned with the detection and recognition of the pathogen, as well as other mycological aspects.

MATERIALS AND METHODS

Brief case report. A 7-year-old boy with B-cell acute lymphoblastic leukemia presented in shock 2 months after an untreated bone marrow relapse. It was discovered by blood culture that he had polymicrobial septicemia involving several bacterial taxa. Broad-spectrum antibiotics caused tem-

porary improvement, but less than a fortnight later tender erythematous papulopustular lesions with raised necrotic centers appeared on his face, arms, and legs. Biopsy of one of the lesions showed hyphal elements morphologically compatible with *Aspergillus* species (Fig. 1). Culture of the biopsy yielded *F. proliferatum*. Two blood cultures that were drawn 24 h apart appeared clear on immediate microscopic examination, but showed hyphae and oval cells after incubation for 48 to 96 h at 37°C. *F. proliferatum* was obtained on transfer to solid media.

Amphotericin B therapy was begun in combination with flucytosine (FC), even though antifungal susceptibility tests showed the fungus to be resistant to both antibiotics individually (see below). Temporary improvement in the skin lesions and in the general condition of the patient was seen for several weeks; but 3 weeks after reinstitution of chemotherapy for leukemia, deterioration began again, with bacterial blood sepsis and new *Fusarium* skin lesions. *F. proliferatum* was recovered from the 2-month-old central venous line tip and from urine of the patient. Rifampin was added to the antifungal regimen of the patient, but he died of respiratory failure. Death occurred about 2 months after the onset of disseminated *Fusarium* infection. A postmortem examination was not performed.

Isolation and identification of the fungus. The *Fusarium* isolates were recovered from biopsied skin on blood agar (5% horse blood in a Columbia agar [GIBCO Diagnostics, Madison, Wis.] base), Sabouraud dextrose agar (SAB; Difco Laboratories, Detroit, Mich.), Levinthal agar (a 1:1 mixture of [i] brain heart infusion broth [GIBCO], with the addition of 10% [vol/vol] horse blood, and [ii] a solution containing 18 g of Proteose no. 3 agar [Difco] per liter and 6 g of Bacto-Agar [Difco] per liter), and McConkey agar (Oxoid Ltd., Basingstoke, England). Incubation was carried out at 30 and 37°C for 3 days. Additional isolations were made from blood in brain heart infusion broth and thioglycolate broth (BBL Microbiology Systems, Cockeysville, Md.) subcultured onto blood agar and SAB. Broth incubations were carried out at 37°C for 2 to 3 days. For identification, subcultures were made onto malt extract agar (41), the malt extract-yeast extract-peptone medium (MYP) described by Bandoni et al. (5), potato glucose agar (PGA), cornmeal agar, and SAB. Microscopic descriptions were prepared based on material from PGA slants and slide cultures on MYP and cornmeal agar. Color names were obtained from Rayner (42).

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FIG. 1. Septate filaments of *F. proliferatum* in subcutaneous tissue. Gomori methenamine silver stain was used. Magnification, $\times 1,000$.

Antifungal susceptibility testing. Susceptibility testing was carried out by broth microdilution and macrodilution to compare the results of the two principal testing methods. The isolate was grown on SAB at 35°C, and the cell pellet was prepared by the method described by Kiehn et al. (26). After it was suspended in sterile water and diluted 100-fold in water, the resulting fungal cell suspension was used without quantitation for the broth macrodilution assay. For the broth microdilution assay, inocula of 5×10^3 and 5×10^4 were prepared in double-strength yeast nitrogen broth (YNB) after they were counted in a hemacytometer.

Broth macrodilution. Mean MICs of amphotericin B, ketoconazole, FC, and rifampin were determined. Amphotericin B was initially diluted in 60% dimethyl sulfoxide to a concentration of $500 \mu\text{g ml}^{-1}$. Further dilutions were carried out in YNB with a range of working concentrations, in doubling dilutions, from 100 to $0.5 \mu\text{g ml}^{-1}$. All doubling dilutions of the three other antifungal agents were made in YNB. The range of dilutions was 200 to $0.01 \mu\text{g ml}^{-1}$ for ketoconazole, 100 to $0.05 \mu\text{g ml}^{-1}$ for FC, and 1,000 to $2.5 \mu\text{g ml}^{-1}$ for rifampin. Each tube contained 1 ml of the appropriate dilution of each antimicrobial agent, to which one drop of the diluted fungal suspension was added from a Pasteur pipette. A growth control without antimicrobial

agents was included for each drug. All tubes were carefully mixed to give an even suspension and incubated at 37°C for 48 h.

The control organism was a laboratory isolate of *Candida albicans* (Robin) Berkh., B3597, with known MICs of amphotericin B of $0.5 \mu\text{g ml}^{-1}$, FC of $0.5 \mu\text{g ml}^{-1}$, and ketoconazole of $50 \mu\text{g ml}^{-1}$. The MIC was recorded as the minimum concentration of antimicrobial agent which suppressed visible growth at 48 h.

Broth microdilution. The four antifungal agents were prepared as described above for the broth macrodilution method. The range of doubling dilutions was the same, except that FC began at $200 \mu\text{g ml}^{-1}$. To each microtiter well was added 0.1 ml of the drug dilution, and the same volume of each inoculum in double-strength YNB was then added. The MIC was recorded as the lowest concentration that showed suppression of visible growth after 48 h at 37°C.

RESULTS

Description of the pathogen. *F. proliferatum*, like many *Fusarium* species, is difficult to identify accurately. The relatively detailed description below should facilitate its identification in the clinical reference laboratory.

Macroscopic features: colony on malt extract agar or MYP agar growing 80 mm in 7 days at room temperature, at first floccose to thinly strigose, soon becoming pannose (i.e., like the surface of woolen cloth) to tufted-floccose, pale pinkish buff, generally with a trace of Vinaceous purple (color 101) at center; reverse creamy buff, with a small zone of Vinaceous purple at center; margin thin, somewhat ragged; soluble pigment and odor lacking.

Microscopic features: hyphae bearing conidiogenous cells initially formed as short lateral branches of the aerial mycelium. These branches later rebranched to build up more complex structures, with each new branch formed at a wide angle to the subtending branch (Fig. 2). Conidiogenous cells were slender, cylindrical phialides, 14.0 to 29.0 (to 51) by 1.5 to 2.5 μm , which tapered to a narrow apex 1 μm in diameter with a minute collarette, sometimes remaining monophialidic but often proliferating subapically to become polyphialidic with two or more conidiogenous loci (Fig. 2 and 3). Successively proliferated single phialides extended to more than 95 μm in length. Conidia (microconidia) were aseptate or exceptionally 1-septate, produced in succession, borne in chains or in viscous headlike masses at the phialidic apices, typically clavate with a truncate base, 4.5 to 10.5 (15.0) by 1.3 to 2.5 (5.0) μm . On older colonies on PGA, a significant proportion of the conidia became inflated, ovate to subglobose-papillate in shape (Fig. 4), measuring 6 to 11.3 by 5 to 11.0 μm , borne in chains or heads intermixed with typical clavate microconidia.

Submerged hyphae often gave rise to lateral phialides or phialidic pegs of 5 to 30 μm in length, producing conidia in heads within the agar medium. Submerged conidia were similar to those produced aerially, but were as much as 18.0 μm long and clavate to clavate-ellipsoidal or allantoid in shape.

Macroconidia were not produced in the cultures examined here. According to Gerlach and Nirenberg (21), some isolates produce these structures after 2 weeks in culture. They are "falcate but rather straight, with a distinct foot cell, usually 3- or 5-septate" and measure 19 to 79 by 2.6 to 5.0 μm .

Chlamydospores absent.

The culture is deposited in the University of Alberta Microfungus Collection and Herbarium as UAMH 5788.

TABLE 1. MICs of four antifungal agents for *F. proliferatum*

Method	MIC ($\mu\text{g ml}^{-1}$)			
	Amphotericin B	FC	Rifampin	Ketoconazole
Macrodilution	>20	>100	>1,000	100
Microdilution				
5×10^3	6.25	>200	500	>200
5×10^4	2.5	>200	1,000	>200

Additional notes. The fungus grew as described above on PGA, but on SAB showed poor development of microscopic structures, with distorted conidiophores and an abundance of atypical conidia. At 37°C, the fungus grew on MYP and blood agar as restricted, tough, glabrous to velutinous colonies. On SAB and 50 mg of cycloheximide per liter at room temperature, moderate growth occurred after a 3- to 4-day lag.

MIC results. The antifungal susceptibility results are given in Table 1. The organism was resistant to all antifungal agents tested. The broth macrodilution technique gave higher MICs than the microdilution method for all antifungal agents tested except ketoconazole. There was no significant inoculum effect demonstrated. The MIC increased only 1 doubling dilution from the lower to higher inoculum for amphotericin B and rifampin.

DISCUSSION

Significance of infection. The infection caused by *F. proliferatum* was typical of disseminated infections caused by

FIG. 2. Branching conidiogenous structures of *F. proliferatum* showing proliferating phialides and clavate microconidia with truncate bases.

FIG. 3. Proliferating phialide (arrowhead) and monophialide of *F. proliferatum* with typical microconidia. Magnification, $\times 1,000$.

Fusarium species (these infections are frequently termed fusariosis [4]). This was true of its clinical presentation, its microscopic presentation, and the nature of the underlying disease which permitted its occurrence. Skin lesions showed profuse development of thin, septate, branching hyphal elements (Fig. 1) that were highly similar to the hyphal elements seen in disseminated *Aspergillus* infections. This *Aspergillus*-like appearance of structures seen in histological preparations is common in *Fusarium* infections (53). Thus, when *Fusarium* infection is being distinguished from *Aspergillus* infection, the histopathological study must be combined with the study of isolated cultures (50). Fluorescent antibody staining and other immunohistochemical techniques may also be used to assist in the distinction (36).

F. proliferatum, although not previously reported as an agent of human disease, is closely related to *F. verticillioides*, which has been reported on several occasions. With its rapid growth rate and tolerance of body temperature, it has a pathogenic potential to cause severe infections in immune-deficient individuals.

Recognition of *F. proliferatum* in pure culture. *F. proliferatum* isolates frequently fail to produce macroconidia in pure culture, and may be confused with *Acremonium* Link: Fr. (*Cephalosporium*) species. However, *F. proliferatum* can be

FIG. 4. Swollen microconidia (arrowheads) produced on PGA at 14 days shown with typical clavate microconidia. Magnification, $\times 400$.

distinguished from *Acremonium* species by its fluffy or pannose appearance, rapid growth, wide hyphae, and proliferating phialides. Only one *Acremonium* species, *A. furcatum* (F. & R. Moreau) ex W. Gams, possesses the latter structures (17), and it forms slow-growing, powdery, cream-colored colonies with small, ellipsoidal conidia that are never borne in chains. Other *Acremonium* species in general are relatively slow-growing (<35 mm in diameter in 10 days on malt extract agar or oatmeal agar [17]) and possess narrow hyphae (mostly <2 mm in diameter). The colonies are usually low and moist or powdery, or at most matted-cottony, and not deeply cottony or pannose (17).

F. proliferatum is distinguished from other *Fusarium* species by the combination of several characters: (i) the presence of proliferating phialides (polyphialides); (ii) the tendency to bear conidia in chains, especially under conditions of reduced water activity (best observed on the media described below); (iii) the strictly clavate shape of the majority of aurally formed microconidia; (iv) the truncate base of the microconidia, a feature that correlates with the ability to form chains; (v) the frequent production of large, ovate microconidia in older cultures on PGA and similar media; and (vi) the complete absence of chlamydospores.

F. proliferatum may be difficult to identify with confidence unless the formation of microconidial chains can be observed. In some isolates, these chains may be difficult to induce; when this is so, colonies should be subcultured on 1.5% water agar or carnation leaf agar (13) supplemented (in either case) with 4 to 8 g of KCl per liter (14). These media greatly accentuate chain formation.

The similar *F. verticillioides* (*F. moniliforme* sensu stricto), the best-known member of the section *Liseola*, produces microconidia in chains but does not possess proliferating phialides. *F. sacchari*, a related plant pathogenic species reported from human eye infections (54), gives rise to proliferating phialides, but produces clavate to ellipsoidal (not strictly clavate) microconidia only in slimy heads. These microconidia, unlike those of *F. proliferatum*, do not possess a flattened base. Another member of the section *Liseola*, *F. anthophilum*, produces a mixture of pyriform and

cylindrical to allantoid microconidia in slimy heads on polyphialides. It is ruled out primarily on the basis of microconidial shape. *F. chlamydosporum*, a member of the section *Sporotrichiella*, produces polyphialides which bear spindle-shaped microconidia in heads. Unlike *F. proliferatum* and other members of the section *Liseola*, it produces abundant chlamydospores in the medium. The ubiquitous *F. oxysporum* (section *Elegans*) also produces chlamydospores, although the formation of these structures may be delayed. In addition, it produces ellipsoidal to curved microconidia in heads on characteristic short monophialides, and generally produces large numbers of robust macroconidia pointed at both ends (use of SAB is not recommended!). *F. proliferatum* can be compared with additional *Fusarium* species by reference to current taxonomic summaries (12, 21, 34).

Taxonomic considerations. Before the publication of a critical review of *Fusarium* section *Liseola* by Nirenberg (35), *F. proliferatum* isolates were generally classified under the name *F. moniliforme* (sensu lato). This name was also used to refer to several other *Fusarium* taxa now known to be reproductively intersterile (28). According to Nirenberg (35), the name *F. moniliforme*, as nomenclaturally typified, is a later synonym of *F. verticillioides*. The name *F. (Oospora) verticillioides* is based on a protologue that lacks reference to macroconidial structures, as well as authentic herbarium material in which macroconidia have not been discovered. This has led to a dispute over the appropriateness of combining this name into the genus *Fusarium*. Arguments for the continued use of *F. moniliforme* sensu stricto, as opposed to *F. verticillioides*, have been outlined by Neish and Leggett (33), Nelson et al. (34), and Ajello et al. (2). The same arguments would also leave *F. (Cephalosporium) proliferatum* without a correct name at the rank of species, and the organism could only be referred to as *F. moniliforme* var. *intermedium* Neish et Leggett (33). We agree with Gams (18), however, that *F. verticillioides* and *F. proliferatum*, although both originally based on microconidial states, are correctly interpreted as names in the genus *Fusarium*. The fact that the name *Fusarium* is primarily associated with the macroconidial state cannot be disputed, but at the same time there seems to be little basis for the use of any name other than *Fusarium* for the microconidial state. This state is invariably recognizable as an element of a *Fusarium* isolate (17); it is produced by the same mode of conidiogenesis as the macroconidial state; and most importantly, it often intergrades with the macroconidial state in size and shape. Debate on the matter is ongoing (2, 46) and has important implications for the nomenclature of all pleomorphic fungi (19), including members of the microconidium-producing dermatophyte genera.

Our examinations of previous reports of *F. moniliforme* as an opportunistic human pathogen have uncovered no reports which appear to pertain to *F. proliferatum*. In all cases in which *F. moniliforme* strains were adequately described or illustrated, the fungus under observation was clearly *F. verticillioides* (2, 10, 39, 50, 53).

F. verticillioides, and not *F. proliferatum*, is also the *F. moniliforme* segregate involved in several experimental studies in which leukoencephalomalacia has been induced in equine animals (27, 29) and in a recent case of mycotic pneumonia in a captive alligator (16). Two of us (J.K., R.C.S.), however, have previously examined a *F. proliferatum* strain that was associated with the vascular invasion of an immunosuppressed patient. Unfortunately, we were unable to obtain complete clinical data on this case. It seems

likely, however, that *F. proliferatum* occurs occasionally as an unrecognized opportunistic pathogen.

Antibiotic susceptibility and pathogenicity. The resistance in vitro of our *F. proliferatum* isolate to antifungal agents is a phenomenon often seen in *Fusarium* infections. *F. verticillioides* has been found to be resistant to amphotericin B and FC in two cases in which it has been tested (25, 50). More distantly related *Fusarium* species also are often resistant to amphotericin B, but some susceptible isolates have been found (7, 50). Resistance to FC appears to be universal within the genus (Richardson et al., submitted). Imidazoles have not been sufficiently tested to permit generalization, but it is worth noting that the *F. verticillioides* isolate studied by June et al. (25) was susceptible to miconazole, a compound that has not been tested by us. In addition, a single test isolate of *F. sacchari* has recently been reported to be moderately susceptible to itraconazole; representatives of other *Fusarium* species were resistant (49).

An interesting feature of our patient was that partial resolution of the fungal infection appeared to occur after amphotericin B-FC therapy, despite the resistance of the organism to both compounds in vitro. This questionable correlation between in vitro susceptibility and in vivo efficacy is also a common feature of *Fusarium* infections in compromised patients (7; Richardson et al., submitted). This uncertainty may be due to host factors or to technical problems related to the current lack of standardization in antifungal in vitro susceptibility testing methods (32).

It is of potential clinical significance that *F. proliferatum* has recently been shown to produce the mycotoxin moniliformin (sodium or potassium salt of 1-hydroxycyclobut-1-ene-3,4-dione) (29). Grain infected with *F. proliferatum* was shown to be toxic to ducklings when used as a feed. Since some *F. proliferatum* strains produced only small quantities of moniliformin but remained highly toxic, the production of other, unidentified mycotoxins must also be suspected.

Epidemiology. In nature, *F. proliferatum* is found in a variety of soil and plant habitats in both tropical and temperate regions (21, 34, 35). Gerlach and Nirenberg (21) have noted an association with greenhouses, which suggests a potential association with cut flowers in hospitals. In Canada, Summerbell (R. C. Summerbell, Ph.D. thesis, University of Toronto, Toronto, Ontario, Canada, 1985) noted that *F. proliferatum* was among the most abundant fungi occurring in the upper soil layers of a clear-cut forest site. It may, therefore, be associated with the dust that originates from ecologically similar sites.

ACKNOWLEDGMENTS

We thank W. Gams for confirming the identification of *F. proliferatum* and for supplying references. The encouragement and support of R. M. Bannatyne is gratefully acknowledged. The Regional Audiovisual Service, Ontario Ministry of Health, is thanked for assistance in preparing photographs, and Margaret Kwok is thanked for medium preparation.

R.C.S. was partially supported by a Medical Research Council of Canada postdoctoral fellowship.

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