Fusarium

A Newly Recognized Fungal Pathogen in Immunosuppressed Patients

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Two cases of disseminated fungal infection due to *Fusarium* species, that occurred during a 4-month period, are reported. Both patients had a myeloproliferative disorder for which they had received intensive cytotoxic and immunosuppressive therapy, and both died despite treatment with amphotericin B. This report and review of the recent literature suggest that *Fusarium* is emerging as a newly recognized fungal pathogen in immunosuppressed patients.

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THE INTENSIFICATION of immunosuppressive and cytotoxic therapy in patients with cancer, and the widespread use of antibiotics, have resulted in an increased incidence of opportunistic fungal infections which are often fatal.[1] The most common fungal pathogens include *Candida, Aspergillus* and *Phycomycetes* species.[2] Fungi previously considered as harmless contaminants when isolated from human sources, are now emerging as significant pathogens in immunosuppressed patients.[3] *Fusarium* species (sp) belong to this group of newly recognized fungal pathogens and have been rarely reported to cause disseminated disease.[4–9] Two patients with culture- and biopsy-proven invasive infection due to *Fusarium* sp following intensive chemotherapy are described in this report, and the previous experience with infections due to *Fusarium* sp is reviewed.

Case Reports

Case 1

A 29-year-old black man, diagnosed as a case of Philadelphia chromosome-positive benign-phase chronic myelogenous leukemia (CML) in June 1983 received 3 to 6×10^6 units of human leukocyte alpha-interferon units intramuscularly daily. A splenectomy was performed in March 1984 because of acceleration of the disease, and he subsequently received combination chemotherapy with vincristine, doxorubicin, and high-dose dexamethasone (VAD) for lymphoid blastic transformation. This was followed by allogeneic bone marrow transplantation during the second benign phase of the disease, with piperazinedione and total body irradiation as a preparative regimen. In July 1984, he was readmitted with recurrence of the lymphoid blastic transformation. The physical examination was unremarkable. Laboratory tests on admission showed the following: hemoglobin 11.3 g/dl; platelet count $112 \times 10^3/\mu l$; leukocyte count (WBC) $103 \times 10^3/\mu l$ with 93% blasts; normal liver and renal function tests, and a normal chest roentgenogram (CXR). The bone marrow was 100% cellular with 96% blasts, which were peroxidase-negative and TdT-positive. Reinduction chemotherapy with VAD was attempted. By day 5 of chemotherapy, he became neutropenic, and neutrophil counts remained below $<0.1 \times 103/\mu l$ throughout his course. He subsequently developed 2 septicemic episodes due to *Klebsiella pneumoniae* and *Flavobacterium multivorum,* which were treated with appropriate antibiotics. On day 30 of chemotherapy, he became febrile and developed bilateral progressive pneumonia. Amphotericin B, 0.6 mg/kg/day, was added to the antibiotic regimen and was subsequently increased to 1.2 mg/kg/day. Two days later the patient developed a black, necrotic ulcer of the hard palate, followed by left periorbital cellulitis and multiple cutaneous and subcutaneous nodules, 1 to 3 cm in diameter, occurring over the extremities and back (Fig. 1). Sinus films showed bilateral maxillary opacification. Biopsy specimens of the hard palatal ulcer and skin lesions showed branching septate hyphae invading blood vessels, consistent with *Aspergillus* sp or *Fusarium* sp (Fig. 2). Cultures from both tissues, as well as from the material aspirated from the left maxillary sinus, grew *Fusarium oxysporum* susceptible to amphotericin B (minimum inhibitory concentrations: MIC 0.6 $\mu g/ml$). The patient's clinical condition worsened, with progressive pneumonia and enlarging skin lesions, with central necrotic ulcerations despite amphotericin B. The patient's clinical condition deteriorated rapidly and he died on day 44 of chemotherapy from respiratory failure, after a total dose of 550 mg of amphotericin B. Autopsy revealed disseminated fungal infec-

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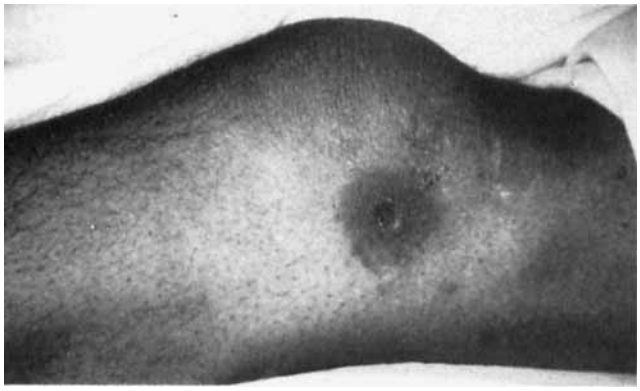

FIG. 1. Skin lesion with necrotic center, surrounding erythema and induration (Case 1).

tion and *Fusarium* sp was cultured from multiple sites. Both lungs were studded with multiple abscesses containing green purlent material. Abscesses were also found in the left epididymis and the left testicle. Infarcts were present in the latter two organs as a result of occlusion of small- to medium-sized arteries by hyphae of *Fusarium*. Examination of the skin revealed multiple indurated, poorly demarcated nodular lesions with dense pigmentation and central discoloration, 1 cm in diameter. Similar lesions were observed in the right wrist, left forearm, right hip, right inner thigh, and left lower extremity ranging in size from 0.8 to 2 cm in diameter. On section of the kidneys, both pelvis showed marked focal dark-brown necrotic regions on the mucosal surface. A left maxillary necrotizing sinusitis was also noted. Fungal hyphae were visualized in microscopic sections into all the above described lesions. There was no evidence of residual leukemia.

Case 2

A 53-year-old black man, diagnosed as a case of multiple myeloma in November 1982, was treated with vincristine, cyclophosphamide, doxorubicin, and prednisone (VACP) combination chemotherapy monthly for 12 months. Treatment was discontinued in November 1983 after the patient achieved a partial remission. Progressive disease was documented in June 1984, and the patient received 3 courses of melphalan and prednisone without objective response. In December 11, 1984, he was started on melphalan 100 mg/m^2 and dexamethasone 100 mg. The physical examination was unremarkable. Laboratory tests on admission showed a hemoglobin of 10 g/dl, a WBC count of $4 \times 10^3/\mu l$, a platelet count of $100 \times 10^3/\mu l$, normal liver and renal function tests and a normal chest x-ray. The bone marrow was 80% cellular with 88% plasma cells. Serum protein electrophoresis revealed an IgG peak of 3600 mg/dl. On day 10 of chemotherapy, he became neutropenic with granylocyte counts remaining below $0.1 \times 10^3/\mu l$ throughout his course. By day 16, fever and bilateral pneumonia developed and the patient was started on trimethoprim-sulfamethoxazole (TMP-SMX) and piperacillin. Renal function subsequently deteriorated with a blood urea nitrogen level (BUN) of 75 mg/dl, and a creatinine of 4.5 mg/dl for which he required peritoneal dialysis. Sequential chest x-rays and arterial blood gases showed no improvement of the pneumonia and a bronchoscopy with alveolar lavage was nonrevealing. On day 23, a 2×1 cm necrotic lesion was noted on the outer aspect of the fourth left finger. Amphotericin B was started empirically at a dose of 15 mg/day. Biopsy specimens of the skin lesion revealed diffuse dermal necrosis with branching septate hyphae invading blood vessels compatible with *Aspergillus* sp or *Fusarium* sp. On days 24, 25 and 26, *Fusarium oxysporum* was cultured from 3 blood cultures and 3 sputum specimens. All *Fusarium* isolates were susceptible to amphoter-

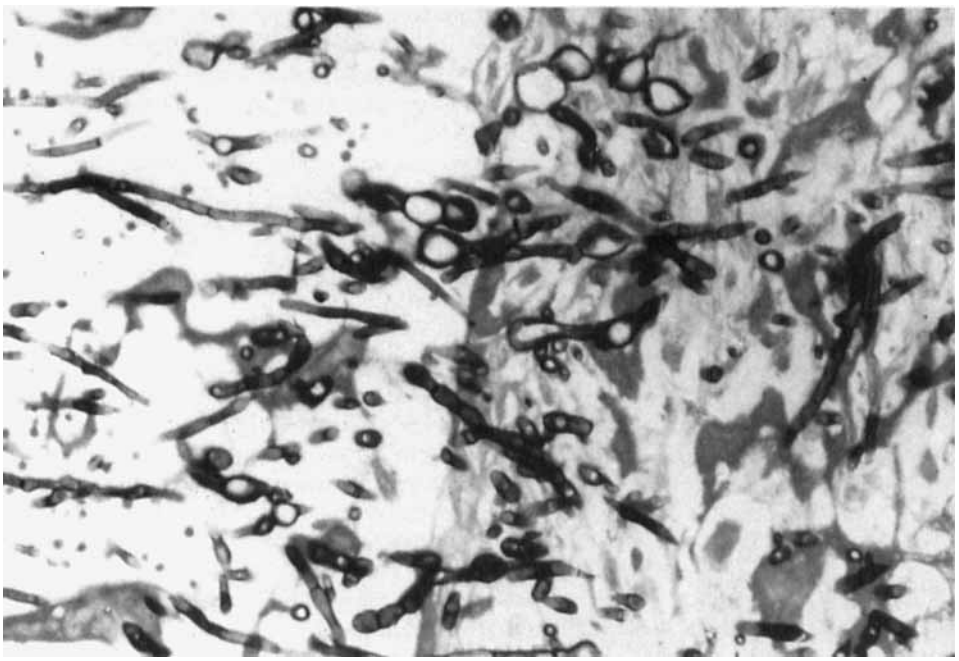

FIG. 2. Branching septate hyphae of *Fusarium oxysporum* in biopsy specimen of skin (Case 1).

TABLE 1. Invasive Infections Caused by *Fusarium* Spp. (Excluding Disseminated Infections)

Site of infection	Ref. no.	Age/sex	Predisposing factors	Treatment	Outcome
Endophthalmitis	17	45/M	Trauma, ocular surgery	Amp B (topical and intraocular)	Enucleation
	18	ND/ND	Trauma, ocular surgery (3 patients)	Antibiotics (topical and intraocular)	1 Failure 2 ND
	19	27/M	Trauma	Vitrectomy, Amp B (systemic and intravitreal) 5-fluorocytosine	Cure
	16	45/M	High-dose steroid	Iridectomy and lens extraction	Enucleation
	15	81/M	Ocular surgery	Vitrectomy, topical steroids	Decreased visual activity
Brain abscess	27	17/F	"Chronic infectious mononucleosis"	Burr hole aspiration Amp B (systemic and intraventricular)	Death
Osteomyelitis	23	17/M	Puncture wound	Amp B	Cure
	22	56/F	Prolonged Ab Rx	Surgery	Cure
Arthritis	24	28/M	Multiple trauma	Amp B	Cure
Peritonitis	26	69/M	Peritoneal dialysis chronic renal failure	Removal of peritoneal catheter; Amp B	Cure
Cystitis	25	9-69/F	ND (7 patients)	None	Spontaneous resolution
Skin and subcutaneous disease	21	14/M	Chronic granulomatous disease	Surgery	Cure
	20	25/F	Renal transplant	Surgery	Cure

Amp B: amphotericin B; ND: not discussed; Ab Rx: antibiotic therapy.

icin B (MIC < 0.6 μg/ml). Amphotericin B dosage was increased to 40 mg/day, and rifampin 600 mg/day was added empirically for possible synergistic antifungal activity. A two-dimensional echocardiogram was normal and a bone marrow biopsy specimen studied with fungal stain and culture was negative. The patient's clinical condition continued to deteriorate, and he died on day 30 of chemotherapy from cardiopulmonary arrest after a total dose of 240 mg of amphotericin B.

Autopsy revealed myelomatous involvement of bone marrow, liver, spleen, and kidneys. The endocardial surface of both right and left ventricles showed multiple dark red nodules from 0.5 to 1 cm in diameter. These nodules were composed of numerous hyphae admixed with fibrin. Similar hyphae were also present in blood vessels deeper in the myocardium. Examination of the lungs showed scattered nodular lesions with sections revealing numerous septate and non-septate hyphae vascular thrombosis. Sections of the esophagus, stomach, and small bowel contained non-septate hyphae in multiple ulcerations, and numerous vascular thrombi were present. Infarcts and vascular thrombosis with hyphae were also documented in the hepatic parenchyma, pancreas, and spleen. Both kidneys contained multiple nodules of 0.7 cm in diameter, as well as vascular thrombosis with hyphae and infarcts of the parenchyma. Tubules were dilated with interstitial edema. The glomeruli were normal. Examination of the brain parenchyma disclosed multiple small abscesses containing green purulent material, less than 1 cm in diameter. Vascular occlusions by thrombi with fungus were present in the brain and the cerebellum with necrosis of adjacent parenchyma. *Fusarium oxysporum, Aspergillus fumigatus,* and *Candida albicans* were cultured from all these sites. In addition, heart blood cultures grew *Fusarium oxysporum* and *Candida albicans.*

Discussion

Fusarium species are filamentous nondermatophyte fungi, which belong to the class Deuteromycetes (Fungi imperfecti), order Moniliales.[6] They are commonly found in soil and are a frequent cause of disease in plants.[10] Systemic illness following the ingestion of *Fusarium*-contaminated cereals was first reported in 1913 in Siberia.[11] At the end of World War II, as many as 1 million people may have been poisoned by infected grain that had been left in the field during the winter.[12] This disease, known as alimentary toxic aleukia, begins with gastrointestinal symptoms and weakness, and culminates in aplastic anemia and death if ingestion of *Fusarium*-contaminated grain persists. This disease results from the effects of the mycotoxin and not from a systemic fungal infection.[11] The species usually involved, *Fusarium sporotrichioides,* is very different from the *Fusarium* species responsible for human infections.

Human infections that may be caused by *Fusarium* sp are usually limited to superficial mycosis, mycotic keratitis, or superficial burn wound infections.[8,13,14] Infection of deep tissues including endophthalmitis,[15-19] skin and subcutaneous infection,[20,21] osteomyelitis,[22,23] septic arthritis,[24] cystitis,[25] peritonitis,[26] and brain abscess,[27] have been reported in patients with a break in the skin or an underlying immunosuppressive condition (Table 1).

Only 11 cases of disseminated infection due to *Fusarium* sp (including our 2 patients) have been described,

TABLE 2. Disseminated Infections Caused by *Fusarium* Species

Reference no.	Age/sex	Underlying diseases (therapy)	Sites of infection	Treatment	Outcome
3	2/M	ALL (CT)	Skin, eye	Amp B	Death
4	2/F	Extensive burns	Skin, heart, kidney, brain	None	Death
5	66/F	Myasthemia, aplastic anemia	Esophagus, liver, spleen	None	Death
6	32/M	DHL (CT)	Skin, heart, kidneys, lungs, pancreas	None	Death
7	23/M	AML (BMT)	Heart, lungs, spleen, oropharynx	None	Death
8	24/M	Extensive burns	Skin, lung	Amp B	Death
9	31/F	AML (BMT)	Skin, lung	Amp B	Death
9	17/F	ALL (BMT)	Nose, maxillary sinus, lung	Amp B	Death
9	44/M	CML (BMT)	Skin, nose, blood, ? small bowel	Amp B surgery (nose)	Death
Current report Case 1	29/M	CML (CT)	Skin, lungs, epididymis, maxillary sinus, kidneys, testes	Amp B	Death
Case 2	53/M	MM (CT)	Skin, lungs, liver, spleen, kidneys, brain, pancreas, endocardium myocardiu, blood, esophagus, stomach, small bowel	Amp B	Death

ALL: acute lymphoblastic leukemia; DHL: diffuse histiocytic lymphoma; AML: acute myelogenous leukemia; MM: multiple myeloma; BMT: bone marrow transplant; CT: chemotherapy; Amp B: amphotericin B; CML: chronic myelogenous leukemia.

usually in patients with myeloproliferative diseases who are undergoing intensive chemotherapy or in patients with extensive burns (Table 2).[3-9] Seven of these 11 patients had biopsy-proven skin lesions, and a black, necrotic lesion was described in 5. Culture- and biopsy-proven pulmonary invasion by *Fusarium* sp was noted in six patients. In addition to our first patient, only one other patient had maxillary sinusitis due to *Fusarium* sp. One patient had periorbital cellulitis. The patient we are reporting (Case 1) is the first patient in whom a necrotic ulcer of the hard palate was the presenting manifestation of disseminated *Fusarium* infection. The findings of maxillary sinusitis, black necrotic ulcer of the hard palate, periorbital cellulitis, diffuse pulmonary infiltrates, and multiple necrotic skin lesions, are similar to those seen with disseminated aspergillosis or mucormycosis. *Fusarium* infection should be considered in the differential diagnosis of this clinical presentation, and specimens of tissue obtained for histologic diagnosis and culture.

Fusarium species are easily recovered from clinical specimens. They grow rapidly on all fungal media not containing cyclohexamide.[6,7] Microscopic examination reveals the characteristic fusoid macroconidia. The mature macroconidia are also called Phragmospores (by Saccardoan classification). Species differentiation is difficult because of their propensity for rapid morphologic change; however, four medically important species have been recognized: moniliforme, dimerum, solani, and oxysporum.[6] Isolates have been recovered from almost any site, including blood, urine, sputum and bone marrow. Fungal stains show septate, branching hyphae that are indistinguishable from infections caused by other fungi, including *Aspergillus* sp.[6] Like *Aspergillus* sp and *Mucor* sp, *Fusarium* sp have a propensity for vascular invasion, resulting in thrombosis and tissue necrosis. Because of these morphologic similarities, identification of the fungus obtained from cultures is required in order to diagnose *Fusarium* infections in the human host. Also, *Fusarium* may occur with concomitant invasive fungi such as *Candida* and *Aspergillus* species.[20]

The therapy and outcome in *Fusarium* infections are dependent on the degree of invasion of the organism, and the status of the host. Superficial *Fusarium* infections respond to local treatment. Results of treatment of deep infections are difficult to assess in view of the paucity of reported cases. In a number of patients with deep infections, surgical resection of infected tissue, amphotericin B alone, or combined surgical and medical treatment were curative (Table 1). One patient with a brain abscess and meningitis died despite surgery and amphotericin B.

No patient with disseminated *Fusarium* infection survived, even with adequate doses of amphotericin B. Amphotericin B has even been given prophylactically in three cases.[9] This probably is related to the severely immunosuppressed status of these patients. As previously noted, the neutrophil count is a critical factor in determining the outcome of disseminated fungal infections.[28] Elimination of foci of infection has been achieved in a few patients who also had a rise in their neutrophil counts while on amphotericin B.[3,9] Another important factor affecting the outcome of these infections could be the susceptibility of the organisms to antifungal agents. *In vitro* studies show a wide range of variation of sensitivity of *Fusarium* isolates to amphotericin B.[8,9] Amphotericin B remains the mainstay of antifungal therapy. Rifampin is sometimes added on an empirical basis. A newly intro-

duced form of amphotericin B, liposomal amphotericin B, seems to be a promising agent. Both *in vitro* and *in vivo* studies are encouraging.[29-32] Preliminary data from cancer patients with disseminated fungal disease refractory to treatment with free amphotericin B, have shown that the liposomal form was less toxic and resulted in resolution of refractory fungal infection in 3 of 12 patients treated.[33] In addition to antifungal therapy, leukocyte transfusion may be given to some patients with prolonged neutropenic episodes.[34] No controlled studies in humans, however, support the benefit of granulocyte transfusions in proven fungal diseases.

In conclusion, this report serves to emphasize the emerging role of *Fusarium* as a newly recognized fungal pathogen in immunocompromised patients. Physicians caring for such patients should consider this pathogen in the differential diagnosis of invasive fungal infections.

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