Dematiaceous Fungi Are an Increasing Cause of Human Disease

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The dematiaceous fungi appear to be an increasing cause of human disease. At The Methodist Hospital, in Houston, Texas, five cases of serious disease caused by these fungi occurred between 1987 and 1992. Cerebral abscesses with Xylohypha bantiana followed treatment for lymphoma. An infection of the lower extremity with Exophiala jeanselmei var. castellanii followed cardiac surgery. Peritoneal growth of Alternaria tenuissima was a complication of peritoneal dialysis. Cerebral abscesses with Dactylaria gallopava occurred in a liver transplantation patient. A traumatic ankle wound contaminated with dirt led to an infection with Phialophora repens. All patients except the last were immunocompromised at the time of the infection; diabetics and patients on steroids may be at particular risk.

The dematiaceous fungi are a heterogeneous group of organisms unified by their production of melanin pigments. They are widely found in nature but are not common human pathogens. At The Methodist Hospital in Houston, Texas, a 1,500-bed primary and tertiary care hospital and teaching facility of Baylor College of Medicine, five cases of serious disease caused by a variety of dematiaceous fungi occurred between 1987 and 1992. A variety of sites and organisms were involved, and no common mechanism is postulated. Most of the patients were immunocompromised; many had disturbances of carbohydrate metabolism due to diabetes or because of treatment with steroids. These cases are reported here to draw attention to this group of organisms as an apparently increasing cause of disease and also to unusual presentations of disease with Exophiala jeanselmei var. castellanii and Dactylaria gallopava.

The dematiaceous fungi are usually defined as those that have melanin or melanin-like pigment in the wall of the hyphae and/or spores [1]. Invasive disease caused by these organisms is called phaeohyphomycosis [2], from the Greek “phaeo,” meaning dark; it is largely diseases of this class that we will be describing here. More superficial, subcutaneous infection is called chromoblastomycosis and is characterized histologically by pseudopitheliotomatous hyperplasia and the presence of pigmented sclerotic bodies [3–6]. Mycetoma, a tumorous growth of the skin, may also be caused by dematiaceous or hyaline fungi (cumaricoyctomyctoma) as well as by actinomycetes (actinomycocytic mycetoma) [7–9]. An excellent review of the dematiaceous fungi has recently been published [10].

Received 1 May 1995; revised 7 August 1995.

This work was presented in part as abstract no. F-87 at the 92nd General Meeting of the American Society for Microbiology in May 1992 (New Orleans).

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Clinical Infectious Diseases 1996;22:73–80 © 1996 by The University of Chicago. All rights reserved. 1058-4838/96/2201-0013$02.00

The dematiaceous fungi are also increasingly recognized in association with a severe form of sinusitis characterized by a unique histologic picture. Such sinusitis was initially attributed to Aspergillus species and was designated “allergic aspergillus sinusitis” [11, 12]; however, in fact, Aspergillus species are only occasionally found in such cases, and the dematiaceous fungi, especially those of the genera Curvularia, Bipolaris, and Exserohilum, are quite commonly seen [13, 14]. The pathogenetic mechanism in such cases is not well defined, but the condition appears to represent a tissue response (“allergic” response) to the presence of fungi. The disease clinically may act in an invasive fashion, eroding the sinus and extending into the brain. However, the hyphal elements usually are seen only in a characteristic exudate and do not, in the strict pathological sense, invade native tissues. A similar “allergic” response to dematiaceous fungi has been reported to cause pulmonary disease [15]. We have noted an increasing number of cases of sinusitis associated with dematiaceous fungi; these are not included in this report.

The dematiaceous fungi that have been reported to cause phaeohyphomycosis are numerous. Fifty-nine species of 28 genera and three classes are reported in a recent text [1]. In addition to the confusion caused by this wide variety of organisms, some of which are associated with but a single case of disease, the taxonomy and nomenclature of this field undergo constant revision and are controversial (see, for example, [16, 17]). Thus, a single organism may be identified by a variety of names in the recent and historical literature, a circumstance that contributes to confusion for clinicians and for all but the most dedicated mycologists. This review does not attempt to deal definitively with the contentious and difficult questions of mycological classification and nomenclature that have marked the study of dematiaceous fungi, but alternative names or appropriate synonyms will be given in each case.

Methods

The materials were received at the microbiology laboratory and processed routinely for fungal cultures; all isolates were identified by the Fungus Testing Laboratory of the University...
of Texas Health Science Center at San Antonio (Dr. Michael Rinaldi, Director). Our nomenclature follows their reports, modified slightly to meet current usage. The cases are listed in table 1; more detailed discussion follows.

**Case Reports**

**Case 1.** A 70-year-old woman was treated for large-cell lymphoma in 1982 and received chemotherapy and radiation. In 1987 she had a cutaneous infection with *Blastomyces dermatitidis*, which was treated with ketoconazole. Persisting enlarged lymph nodes were biopsied, and Hodgkin’s disease, of unknown type and stage, was diagnosed. She received chemotherapy. The next year a slow decline in mental status began with confusion and lethargy. After several months a CT scan was performed, which showed a cerebellar mass. A biopsy was performed elsewhere, yielding purulent material, and the organism cultured from this was reported to be *Cladosporium bantianum*. The mass was totally excised, and she was treated with flucytosine of unknown dose and duration, but progressive deterioration in level of consciousness and high spiking fevers were noted.

She was transferred to our hospital. A CT scan showed dilatation of the right lateral ventricle with an enhancing area in the region of the foramen of Monro on the right side. An Ommaya reservoir was placed in the right frontal region by ventriculostomy. At this time fungal cultures of a liver specimen, peritoneal fluid, bone marrow, and CSF were negative. No further antifungal therapy was given. Three weeks later the patient was found without pulse or respiration and was pronounced dead. At autopsy the brain had multiple fungal abscesses and hemorrhagic necrosis, involving the thalamus, basal ganglia, fornix, corpus callosum, pons, cerebellum, and cervical cord (figures 1 and 2). Autopsy cultures of brain specimens yielded *Xylohypha bantiana*. No evidence was found of lung involvement or other dissemination.

This case graphically demonstrates the clinical confusion that can be caused by nomenclatural changes in mycology. Presumably, the same infection was reported from different institutions as *C. trichoides* and *X. bantiana*. The organism has been variously called *C. trichoides*, *Cladosporium bantianum*, and *Torula bantiana* and most recently has been classified as *X. bantiana*, with *C. bantianum* as a synonym [18]. This reclassification has been the subject of dispute [1, 19], and cases may currently be reported under either name.

Under its various names, *X. bantiana* is known to be a common source of cerebral phaeohyphomycosis, accounting for ~50% of cases in several series [1]. These infections occur in apparently immunocompetent individuals, especially young males [20–23], as well as in those immunocompromised by steroids [24], cancer [25], transplantation [26], or decreased immunoglobulin levels [27]. Most patients present with mental status changes, and the frontal location is most common [23]. Extension from paranasal sinuses has been reported [28]. Chronic meningitis, without cerebral invasion, has also been demonstrated [29]. Most cases of infection with *X. bantiana* cause CNS disease [23], although a few pulmonary cases have been reported [30].

Skin involvement has been proposed to be a source of cerebral disease, but this has not been demonstrated [31]. Exposure to soil may be a risk factor [23]. The multiplicity of abscesses in many cases argues for a hematogenous spread; a portal of entry, presumably pulmonary, is rarely documented. One case involving a 61-year-old man with lymphopenia and an absence of T-helper cells has been reported [32]. This history is clearly suggestive of AIDS, but this and other reports were published well before the clinical occurrence of AIDS became common, and no HIV status is reported for most of the patients. The outcome of cerebral xylolphyta infection is very poor with antifungal therapy alone, and neurosurgical debridement appears essential for any hope of cure. Even with aggressive surgical and medical treatment, mortality probably exceeds 50% [23].

**Case 2.** A 69-year-old man with unstable angina was admitted to our hospital. He had a 5-year history of adult-onset
Figure 1. Autopsy of the brain of patient 1 revealed a mass of faintly pigmented hyphal elements of *Xylohypha bantiana* (right) occupying the ventricle; ventricular lining cells are seen to the left (stain, hematoxylin and eosin; original magnification, ×100).

Figure 2. Autopsy examination of the brain of patient 1 revealed the hyphae of *Xylohypha bantiana*, well seen in this Fontana-Masson preparation, which stains the melanin (original magnification, ×100).

Figure 3. The small yeast forms and pseudohyphae of *Candida albicans* are on the surface (right) of the leg of patient 2, while the pigmented hyphae of *Exophiala jeanselmei* var. *castellanii* are more invasive, found deeper in the necrotic tissues (left) (stain, hematoxylin and eosin; original magnification, ×10).

Figure 4. Variably pigmented elements of *Alternaria tenuissima* assume unusual forms in the peritoneal cavity of patient 3 (stain, hematoxylin and eosin; original magnification, ×100).

Figure 5. An abscess cavity in the brain of patient 4 is lined by the hyphal elements of *Dactylaria gallopava*, stained black by Grocott-Gomori methenamine-silver nitrate stain (original magnification, ×10).
diabetes mellitus. For three years he had had peripheral vascular disease, with claudication of the calf. Doppler evaluation revealed left aorto-iliac artery obstructive disease and mild right tibial artery obstructive disease. A cardiac angiogram demonstrated severe coronary artery disease. The patient underwent coronary artery bypass grafting with saphenous leg veins and the left internal mammary artery. On postoperative day 6 the patient had a right iliac artery occlusion, which was treated with a right-to-left femoral-femoral bypass. A right common femoral thrombus later developed, and a thrombectomy was performed.

Following thrombolytic therapy, a hemopericardium developed, which required a second sternotomy. Glucose levels and renal function were difficult to control, and peritoneal dialysis was begun. Adult respiratory distress syndrome developed, and inotropic support was required. In the right lower extremity, cyanosis and ischemia developed. Fasciotomy was performed and local treatment was administered, but dry gangrene eventually required an above-the-knee amputation, 26 days after the original cardiac surgery. Cultures of specimens from the leg yielded Exophiala castellanii (now regarded as a variant of E. jeanselmei [33]) and Candida albicans. No other organisms were isolated. The patient’s condition continued to deteriorate, and he died 4 days after the amputation. No antifungal therapy was given. No autopsy was performed.

Pathological examination of the amputated limb showed the skin to be covered extensively with a mixed infection due to Exophiala and Candida species. The morphological appearance was quite striking (figure 3), with invasive pigmented Exophiala hyphae covered with more superficial candidal forms.

The patient’s right leg was compromised locally by a number of factors: peripheral vascular disease, postoperative thrombus formation, and the high levels of peripheral vasoconstriction necessary to support systemic blood pressure. Thus, the limb was ischemic. In addition, the patient had a number of specific systemic problems that may have compromised immune function: he had long-standing diabetes, with very poor glucose control during this episode; he had had massive blood transfusions, known to be immunosuppressive [34]; and he had (terminally) poor renal function, also immunosuppressive. Multiple blood cultures were negative. The sputum, as well as the leg, yielded C. albicans, but no specific features of fungal pneumonia were seen.

E. jeanselmei var. castellanii was at one time considered a new species, E. castellanii [35]. It is commonly regarded as a variant of E. jeanselmei [33]. To our knowledge, no other cases of human disease with this variant have been reported. E. jeanselmei is a relatively common cause of subcutaneous and skin infections [36]. For example, its presence in a hand infection in a renal transplantation patient receiving steroids has been reported. This lesion healed completely with administration of fluconazole [37]. In a boat-builder who was receiving steroid therapy for a rheumatic condition, knee and elbow lesions developed that yielded both Phialophora richardsiiae and E. jeanselmei. In this case, the former organism was regarded as the primary pathogen and the latter as a copathogen or contaminant, but no basis for this opinion was given [38]. The histologic findings in both of these cases were similar to ours: scattered, pigmented hyphae and spores within a dense inflammatory infiltrate. The growth in our case was more luxuriant, presumably because of poor circulation.

Endocarditis and arthritis have also been reported, in an unusual case following injection of steroids into the knee [39]. In patients with AIDS, E. jeanselmei may rarely cause esophagitis that is difficult to distinguish from candidiasis [40]. Wangiella dermatitidis, a closely related species also called Exophiala dermatitidis [1], usually causes more systemic and neurotropic infections [41]. W. dermatitidis is also increasingly recognized in patients with cystic fibrosis [42, 43], and in some unusual cases it may cause lung disease in those without cystic fibrosis [44]. The pathogenicity of the organism in patients with cystic fibrosis is controversial; some investigators believe that its presence represents colonization rather than disease. Exophiala mansonii has also been reported to cause synovitis in a renal transplant recipient [45] and skin disease following possible trauma in a patient receiving chemotherapy [46]. Skin lesions due to Exophiala pisciphila [47] as well as Exophiala spinifera [4] have been reported. The morphological similarity of E. spinifera and E. jeanselmei has led to the development of an exoantigen assay [48] that may be useful in some cases.

Case 3. A 34-year-old man with renal failure who was being treated with continuous ambulatory peritoneal dialysis (CAPD) had chronic peritonitis and small-bowel obstruction. Culture specimens from a surgical exploration of the peritoneum yielded Alternaria tenuissima. Histology of the surgical specimen revealed numerous large pigmented hyphae in the peritoneal fluid and fibrinous exudate (figure 4). He received 910 mg of amphotericin B while hospitalized and was well at discharge. Administration of a total of 2.5 g of amphotericin B was planned.

Individuals being treated with CAPD are at increased risk of fungal infections in several ways. The occurrence of uremia or renal failure itself causes a state of immunosuppression, as leukocyte function is impaired. In addition, the indwelling catheter used for peritoneal dialysis provides an easy port of entry in these patients. Renal transplant recipients, of course, are immunosuppressed and thus—like other transplant recipients—are subject to fungal infections [45, 49, 50].

As many as 60% of patients undergoing CAPD have peritonitis in the first year [51]. In most series, three-fourths of the organisms are gram-positive, approximately one-fourth are gram-negative, and less than 5% are fungi [51]. Among these fungi, Candida is the most common organism, and both Candida parapsilosis and C. albicans are frequently reported [52]. Other, more unusual yeasts and molds have also been reported, including Trichosporon beigelli [53] and the dematiaceous Lecythophora mutabilis (previously called Philalophora mutabilis) [54] and Curvularia species [53, 55, 56]. Alternaria species have been reported in two previous cases [57, 58]. Fungal peritonitis may follow antibiotic therapy, and it is unclear if
this sequence simply reflects the common co-occurrence of bacterial and fungal infections or if antibiotic therapy is an independent risk factor for fungal infections [52]. Diabetics undergoing CAPD may be at particularly elevated risk of fungal peritonitis [52].

Case 4. A 59-year-old man presented with mental status changes. Two years previously he had received a liver transplant for cirrhosis of unknown etiology, and at the time of presentation there was evidence of severe rejection despite the administration of steroids and other immunosuppressive therapy. Two months before this presentation, an episode of bacteremia and pulmonary infection with Nocardia asteroides had occurred; it had been treated and apparently resolved. At the current presentation, he was lethargic and confused, with right hemiparesis. A CT scan revealed multiple cerebral lesions, and a biopsy of one of the brain lesions was performed. Histologic examination showed extensive granulomatous inflammation and cavity formation (figure 5), and cultures yielded D. gallopava. Other specimens, from the lung, yielded N. asteroides. The patient was treated with 2.5 g of amphotericin B but succumbed to liver failure in ~2 months. At autopsy, no residual fungal disease was present in the brain, as determined by culture and histology. Only a limited autopsy was permitted, and the lungs were not examined.

The taxonomy and nomenclature of the Dactylaria genus and the closely related Scolecobasidium genus have been controversial. Mycologists de Hoog and van Arx combined D. gallopava, Scolecobasidium humicola, and Scolecobasidium tschawyczseae to make a new genus, Ochroconis, but this classification has not been entirely accepted [1, 59]. Salkin and Dixon proposed, on morphological grounds, that D. gallopava be regarded as Dactylaria constricta var. gallopava, while Scolecobasidium constrictum be regarded as Dactylaria constricta var. constrictum [60]. This assignment has been contested by others, who argue that the antigenic and physiological differences between the organisms are sufficient to retain two species: D. gallopava and S. constrictum [61].

Two cases of cerebral involvement with D. gallopava, both in immunocompromised hosts, have been previously reported. One involved a patient from North Carolina with large-cell lymphoma, in whom a single right frontal lesion developed [62]. The patient had previously had N. asteroides infection, which had presumably been cured by the time of the dactylaria infection. In this report, the organism is called Ochroconis gallopavum. The second case involved a diabetic patient with T-cell chronic lymphocytic leukemia, who had widely disseminated D. gallopava infection [63]. Both patients died. Subcutaneous D. gallopava (reported as O. gallopavum) infection has also been reported to occur in a patient with myeloid leukemia, in Japan [64]. S. constrictum (called Ochroconis constrictum in the publication) was also indirectly reported as a cause of a brain abscess in a diabetic patient from Louisiana [64]. All of these patients were immunocompromised, and most had some disturbance of carbohydrate metabolism, via either primary diabetes or steroid treatment. A propensity for infection in the southeastern United States has been noted, but this organism has also been isolated from thermal pools in Yellowstone National Park and thermal effluents of nuclear reactors [64, 65].

It is interesting that a number of other cases of cerebral phaeohyphomycosis with various species have been reported in association with N. asteroides [20, 27, 32, 62]. While underlying immunosuppression may be suspected in all these patients, the association seems stronger than might be expected by chance. Presumably the patients, already compromised in some way, acquired a nocardia infection (pulmonary or disseminated) that may have predisposed them to the acquisition of a fungal infection, possibly acquired initially through a pulmonary source. Such a pulmonary origin is the frequently presumed but rarely documented portal of entry for the dematiaceous fungi when they are found in other areas of the body. The previous occurrence of nocardia infection may delay diagnosis of the fungal infection, as the patient may receive treatment for presumed recurrence of nocardia infection.

Case 5. A 41-year-old man sustained a forklift injury to his left ankle. The wound was contaminated by dirt. There was no evidence that he was immunocompromised, and he was HIV-negative. Following the injury, he had a bone chip surgically removed. The ankle gradually developed fluctuant and draining abscesses. Cultures 3 months after the accident yielded only rare Bacillus species, which were regarded as contaminants. Fungal cultures were not performed at this time. He was treated with minocycline and his wounds healed well.

Five months post-injury a purulent discharge was noted again, and cultures of specimens from the surgical debridement yielded methicillin-resistant Staphylococcus aureus but were negative for other bacteria, fungi, or acid-fast bacilli. He was treated with a 6-week course of vancomycin. The wound continued to drain and form abscesses, and osteomyelitis developed. Cultures of specimens from surgical debridement, now 10 months after the injury, yielded Phialaphora repens, Sporothrix schenckii, and no bacteria. Histology revealed rare pigment-sclerotic bodies in a dense inflammatory infiltrate. The wound was surgically debrided and the patient received a total of 750 mg of amphotericin B before this drug was withdrawn because of renal toxicity. The patient healed well. At this time the patient’s therapy was switched to oral ketoconazole (200 mg b.i.d.), which was to be administered for several months.

Both S. schenckii and P. repens were isolated from the last debridement specimen. However, there was no histologic evidence of sporothrix infection, while the sclerotic bodies seen with a dematiaceous organism such as Phialophora were demonstrated. Moreover, the lymphatic involvement characteristic of sporothrix infection was not seen. The clinical and histologic evidence thus support the pathogenicity of P. repens.

P. repens is a cause of bluish staining in timber and is commonly found in nature. Other species of Phialophora (richardsiae, parastica, verrucosa, and mutabilis) are more commonly reported as the cause of human disease, including phaeohyphomycosis, keratitis, and disseminated disease. P. repens was reported in 1975 as a cause of a subcutaneous granuloma-
tous scalp nodule in an African patient with lepromatous leprosy who was being treated with corticosteroids [66]. In a second case, P. repens was cultured from the dorsum of the hand of an otherwise healthy Japanese man [67]. No specific trauma was reported or could be recalled in either previously published case.

In our case, fungal cultures were not performed when post-traumatic infection was first noted, and they were negative when first done 5 months later. Fungal organisms were not identified in several surgical specimens, although they were not suspected and were not specifically sought. Moreover, because tissue response is nonspecific, the sensitivity of histopathology is poor. The history of initial trauma, the indolent course, and the histology suggest that a Phialophora species caused disease from the beginning, and the negative cultures at 3 months may have been due to the very small number of fungal organisms present in the tissue, embedded in a dense fibrous matrix. It is less likely that the wound may have been secondarily infected with this fungus.

Discussion

In our series we have two infections of the CNS, one peritonal infection, and two infections of the lower extremities. One extremity infection appeared to be a classic example of dirt contamination of a penetrating wound; most of the other cases involved invasive disease. All of these cases of invasive disease occurred in patients who had some source of immune compromise, particularly cell-mediated immunity; these conditions ranged from immunosuppressive therapy for transplant rejection to peritoneal dialysis. Despite the relatively large number of patients with AIDS seen at our hospital, no cases in this series involved patients with AIDS, and such cases have not often been reported by other investigators.

Of particular interest is the frequent presence of a disturbance in carbohydrate metabolism, due to frank preexisting diabetes or the use of steroids, both of which are known to disturb carbohydrate metabolism as well as cell-mediated immunity. An association of diabetes with other fungal infections, notably candidal infections and invasive disease with the zygomycetes, has long been noted, although the mechanism is not entirely clear (see review in [68]). Many other reports as well have documented infections with dematiaceous fungi in diabetic patients [36, 49, 54–57, 67, 69, 70]. Possible mechanisms include impaired neutrophil, macrophage, and complement function in the diabetic [71].

An additional large group of infections involves those receiving steroids [24, 30, 37–39, 45, 47, 50, 64, 66, 70, 72–74]; some of these patients had no other known immunosuppressive conditions. An experimental model has shown a direct effect of steroids on CNS infections with X. bantiana [75]. With regard to steroids, of course, we must consider the underlying disease that led to treatment with the drugs, as well as the direct immunosuppressive role of the steroids themselves; several mechanisms, including those related to carbohydrate intoler-

ance as well as other factors in cell-mediated immunity, may be involved. Our report confirms the observation of other investigators [76] that these fungi are increasingly likely to be the causes of human disease, and it suggests that diabetic patients or persons receiving steroids may be particularly susceptible.

The dematiaceous fungi, many of which are common in the environment, cause disease only rarely, usually in the compromised host. As our patient population consists more and more of such persons, we must look carefully to diagnose these still-unusual fungal infections.

Acknowledgments

The authors appreciate the clinical information provided by the physicians caring for these patients, especially Drs. Major Bradshaw, Victor Fainstein, Richard Harris, Tobias Samo, and Temple Williams.

References


