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Invasive *Nattrassia mangiferae* Infections: Case Report, Literature Review, and Therapeutic and Taxonomic Appraisal

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We report on a case of subcutaneous infection of the arm caused by the coelomycetous fungus *Nattrassia mangiferae* (formerly *Hendersonula toruloidea*) in a steroid-dependent diabetic man with chronic obstructive lung disease. The man was a resident of Arizona, where the fungus is known to be endemic on *Eucalyptus camaldulensis* and on citrus trees. Diagnosis of fungal infection was made by observation of narrow hyphal filaments by histopathology of biopsy specimens and isolation of a fast-growing black mold which demonstrated hyphae and arthroconidia of varying widths typical of the *Scytalidium* synanamorph (*S. dimidiatum*). The formation of pycnidia, which at maturity expressed conidia with a central median dark band, allowed for the confirmation of the isolate as *N. mangiferae*. Remission of the lesions occurred following intravenous therapy with amphotericin B, followed by topical clotrimazole treatment. We use this patient's case report as an opportunity to review the literature on cases of deep infection caused by *Scytalidium* species, to evaluate the antifungal susceptibilities of a spectrum of *Scytalidium* isolates, and to review the taxonomy of *Scytalidium* species isolated from human infections.

Hendersonula toruloidea Nattrass is a dematiaceous coelomycete causing dieback and wilt of primarily woody hosts in tropical and subtropical regions worldwide (52). Nattrass (47) observed that the fungus was polymorphic on the plant host, forming multiloculated pycnidia immersed in the host tissue and a *Torula* stage consisting of spores formed by fragmentation of brown hyphae. Cultures established from infected plant tissue invariably produce arthroconidia, while special growth conditions are usually required to produce pycnidia. Sigler and Carmichael (57) suggested that the dominant arthroconidial stage should be referred to *Scytalidium* Pesante. Sutton and Dyko (61) renamed the pycnidial stage as *Nattrassia mangiferae* (H. & P. Sydow) Sutton and Dyko. They also proposed the name *Scytalidium dimidiatum* (Penz.) Sutton & Dyko for the arthroconidial synanamorph and suggested that it might be identical to *Scytalidium lignicola* Pesante, the type species of *Scytalidium*. Each of these names is in current use for agents of human infection.

Since Gentles and Evans (17) first reported on *N. mangiferae* isolates causing superficial dermatomycosis and onychomycosis clinically indistinguishable from typical dermatophyte infections, a number of reports have concerned patients who had immigrated to the United Kingdom (3, 23, 42, 43). Other papers documented the incidence of infection in residents of areas where the fungus was known to be endemic (20, 21, 30, 31). In North America, the fungus is being seen with increasing frequency in the dermatological diagnostic laboratory (28, 60), but relatively few cases of infection occur in individuals who have no history of residence or travel elsewhere (14, 27), despite the cosmopolitan distribution of the fungus on various hosts, including *Arbutus*, *Ficus*, *Citrus*, *Juglans*, and others (11). Only rare reports of infection have been attributed to *S. lignicola* (7, 8, 13).

Reviews of the literature on *N. mangiferae* infections and on infections due to *Scytalidium* species recently have been provided by Frankel and Rippon (14) and Moore (44), but there have been few reports of deep infections. Reports have involved mycetoma (9) and subcutaneous abscesses of the foot (65), facial lesions (35–37), fungemia and abdominal abscesses (2), endophthalmitis following trauma (1), and abscess following trauma to the base of a finger (34). Diabetes has been the underlying condition in two cases involving subcutaneous abscess of the ankle (8, 39) and one case involving the maxillary sinus (40, 41). In this report, we describe a similar case of subcutaneous fungal infection in a diabetic male; the histopathology, mycology, and in vitro antifungal susceptibility of the organism; and our experience with treatment. We use this patient's case report as an opportunity to evaluate the antifungal susceptibilities of a spectrum of *Scytalidium* isolates, to critically review the taxonomy of *Scytalidium* species isolated from human infections, and to consider the most appropriate name for the isolated fungus. We contend that the *Scytalidium* synanamorph of *N. mangiferae* (*S. dimidiatum*) can be distinguished from *S. lignicola* by morphological differences and that the latter species has not been reliably documented as the cause of human infection.

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MATERIALS AND METHODS

Case report. A 73-year-old white man was admitted to the Veterans Affairs Medical Center in Tucson, Ariz., with a myocardial infarction complicated by a

bacterial nosocomial pneumonia. His past medical history was remarkable for previous myocardial infarctions, congestive heart failure with peripheral edema, steroid-dependent (prednisone at 20 mg/day) chronic obstructive pulmonary disease, and type II diabetes mellitus treated with insulin. On his eighth hospital day, he reported pain centered around his left medial elbow. Within 2 days, multiple pustules, 1 to 3 mm in size, were noted in the area of discomfort. Cultures of the lesions were obtained, and local care consisting of warm-water soaks and dressing changes was instituted. Despite these measures, his left upper extremity became inflamed, and there was an increase in the size and number of pustules. Treatment with intravenous vancomycin had no effect. On the 14th hospital day, the cultures obtained 4 days earlier began to show a fungus.

At that time, physical examination revealed an elderly white man with a normal temperature. He had "tissue paper" skin with multiple scattered ecchymoses consistent with chronic steroid use. His left upper extremity was warm, erythematous, tender, and edematous with scattered multiple pustules extending from the mid-forearm to the mid-upper arm. Purulent material could be expressed from the pustules. Laboratory studies were remarkable because of a leukocyte count of 14,700/mm^3 with 89% granulocytes, 3% monocytes, and 8% lymphocytes. The blood glucose level was well controlled.

Because of the availability of preliminary culture results, topical 1% clotrimazole cream was added to the patient's regimen. Five days after the appearance of the skin lesions, a punch biopsy specimen was obtained and was interpreted as showing septate fungal elements. Culture of this specimen likewise grew a fungus, and subsequently, both isolates were identified as *N. mangiferae*/*S. dimidiatum*. On the 16th hospital day, therapy with amphotericin B was initiated. Several fluctuant areas measuring 1 by 2 cm had developed; they were lanced, and 3 to 5 cm^3 of pus was drained from each. Fingernails and toenails from all four extremities were pared and shavings were submitted for fungal culture, but *N. mangiferae* was not recovered from these sites.

By the 53rd hospital day he had received 530 mg of amphotericin B and his arm was markedly improved. Arrangements were made for discharge to home and continuation of his amphotericin B as an outpatient. Interestingly, on the day of discharge, a repeat skin biopsy was performed and the fungus was again isolated in culture.

While at home the patient discontinued topical clotrimazole. Multiple pustules reappeared and viable fungus was obtained from them. Topical clotrimazole was reinstituted, with resolution of the superficial lesions.

Mycology. A swab (Transwab Transport System; Medical Wire and Equipment Co.) from an elbow pustule was originally submitted for routine bacterial cultures. The swab was inoculated onto plates of Levine's eosin methylene blue and azide blood agar (both from BBL Microbiology Systems, Cockeysville, Md.), trypticase soy agar with 5% sheep blood (BA), and into thioglycolate broth to which hemin and vitamin K were added (both from MicroBio Products, Inc., Tempe, Ariz.). All cultures were incubated at 35°C in a 5% CO_2 atmosphere. Additionally, anaerobic cultures (BBL GasPak Plus) were set up on BA and brucella agar (MicroBio Products, Inc.), and the plates were incubated at 35°C. When a mold became evident, it was subcultured onto duplicate plates of potato dextrose agar, lactrimel agar, Sabouraud dextrose agar (SDA), brain heart infusion agar with gentamicin, and mycobiotic agar (all from MicroBio Products, Inc.), and the plates were incubated at room temperature (ca. 25°C) in an ambient atmosphere and at 35°C in a 5% CO_2 atmosphere. Skin biopsy specimens, both ground with saline and unground, were placed on various mycological media selected from among the media described above and were incubated similarly.

For identification, the isolate was sent to the Mycology Reference Laboratory, Audie L. Murphy Memorial Veterans Hospital, San Antonio, Tex.; Mycology Unit, Centers for Disease Control and Prevention, Atlanta, Ga.; and University of Alberta Microfungus Collection and Herbarium (UAMH), Devonian Botanic Garden, Edmonton, Alberta, Canada, where it was deposited as strain UAMH 6673. To promote the development of the pycnidial stage, the isolate was grown on Pablum cereal agar and V8 agar (28) and on pieces of lemon and banana peel. Five-millimeter-wide strips of peel, sterilized by autoclaving in glass petri dishes with 5 ml of water at 121°C for 15 min, were inoculated with fragments of mycelium and were incubated in moist chambers at room temperature in an ambient atmosphere in daylight.

Histopathology. Punch biopsy specimens of skin were cut into sections 5 to 6 μm thick and were stained with hematoxylin and eosin, Gomori methanamine silver nitrate (GMS), and periodic acid-Schiff (PAS) stains.

Antifungal susceptibility testing. The case isolate and 16 additional isolates of *N. mangiferae* and 4 isolates of *Scytalidium hyalinum* from human sources were tested to determine their susceptibilities to antifungal drugs. The ex-type isolate (isolate derived from the type specimen) of the normally nonpathogenic wood decay fungus *S. lignicola*, which has been confused with *N. mangiferae*/*S. dimidiatum*, also was tested not because of any anticipation that *S. lignicola* will be shown to be an etiologic agent, but rather to determine if the testing would yield characters that would aid in its differentiation from *N. mangiferae.*

Tests were performed by previously described macrodilution methods (50, 53). Briefly, the test isolates and the standard control organisms (*Saccharomyces cerevisiae* ATCC 36375 and *Candida tropicalis* ATCC 13803) were grown for 48 h at 25°C on SDA and were then suspended in sterile distilled water. The suspensions were adjusted spectrophotometrically to 90% transmission at 530 nm and were diluted 10-fold. Concentration ranges were as follows: for amphotericin B (E. R. Squibb & Sons, Princeton, N.J.), 0.14 to 18.6 μg/ml; for flucytosine (5-FC; Hoffmann-La Roche Inc., Nutley, N.J.), 10.09 to 322.75 μg/ml; for ketoconazole (Janssen Pharmaceutica, Piscataway, N.J.), 0.0125 to 12.8 μg/ml; for fluconazole (Pfizer Pharmaceuticals, New York, N.Y.), 1.25 to 80 μg/ml; for miconazole (Janssen Pharmaceutica), 0.6 to 20 μg/ml; and for itraconazole (Janssen Pharmaceutica), 0.018 to 10 μg/ml. Amphotericin B was tested in antibiotic medium 3 (Difco, Detroit, Mich.), and other antifungal agents were tested in Synthetic Amino Acid Medium-Fungal (SAAM-F; American Biorganics, Inc., North Tonawanda, N.Y.). Tubes were inoculated with 50 μl of the inoculum suspension and were incubated at 25°C for 48 h. MICs and minimum lethal concentrations (MLCs) were measured at 24 and 48 h. The MIC was defined as the lowest concentration of antifungal compound in which growth was not observed. The MLC was determined by dispensing and streaking 10 μl of broth from those tubes exhibiting no growth onto SDA plates for each concentration. The MLC was defined as the lowest concentration of antifungal compound resulting in three or fewer colonies on the SDA plate. All tests were run in duplicate and gave essentially identical results.

RESULTS

Histopathology. Sections through sun-exposed hair-bearing skin showed artifactually disrupted epithelium without hyperplasia or inflammation. Within the dermis was a mild inflammatory infiltrate consisting primarily of neutrophils but with occasional lymphocytes and plasma cells (Fig. 1). No granulomas were seen. PAS and GMS stains revealed short fragments of unbranched hyphae which measured 1.0 to 1.5 μm in width (Fig. 1). No pigmentation of the hyphae was seen in PAS-stained sections.

Mycology. From the original routine bacterial cultures, coagulase-negative staphylococci were isolated after 24 h. Within 72 h, both the aerobic BA and eosin methylene blue agar showed a mold. On mycological subcultures and later direct cultures of skin biopsy specimens, growth occurred at both temperatures on all media without cycloheximide and was more luxuriant on the lactrimel agar.

The fungus was identified as *N. mangiferae*/*S. dimidiatum* (form 1) (43, 44, 57) by its colonial and microscopic features. The colonies grew rapidly, filling the petri dish within 4 to 7 days, becoming olivaceous grey to black and overlaid with aerial strands of greyish black mycelia. The reverse was initially buff but darkened to a greyish black. Cellophane tape preparations and slide cultures demonstrated septate, branched, subhyaline to dark brown hyphae ranging from 2 to 8 μm in width. Both the narrow and wide hyphae fragmented to form cylindrical or barrel-shaped, subhyaline to dark brown, nonseptate or one-septate arthroconidia (Fig. 2). Pycnidia developed on natural media within 2 to 3 weeks and on cereal and V8 agars after 6 to 8 weeks. Immature pycnidia, when crushed, revealed phialides and conidia which were initially hyaline and ellipsoidal (Fig. 3). Pycnidial conidia differed from the arthroconidia by having tapered ends. At maturity (requiring several more weeks), the pycnidial conidia developed one or two septa and a brown median band, with the upper and lower cells being subhyaline (Fig. 4). They measured 9 to 12.5 μm in length and 3.5 to 5 μm in width.

In vitro antifungal susceptibility. Results of in vitro susceptibility tests indicated that the isolate from the current patient (case isolate) and 20 comparison isolates demonstrated similar patterns of susceptibilities (Table 1). The MICs of most antifungal agents for all isolates were relatively low. As judged by MICs, the case isolate was susceptible to amphotericin B and itraconazole at concentrations which are commonly achieved in patients receiving recommended dosages for invasive mycoses (0.25 to 0.75 mg/kg of body weight daily for amphotericin B and 100 to 400 mg daily for itraconazole) (16, 56). As judged by the MLCs, the isolate was less susceptible to amphotericin B and was resistant to itraconazole.

The remainder of the isolates appeared susceptible to am-

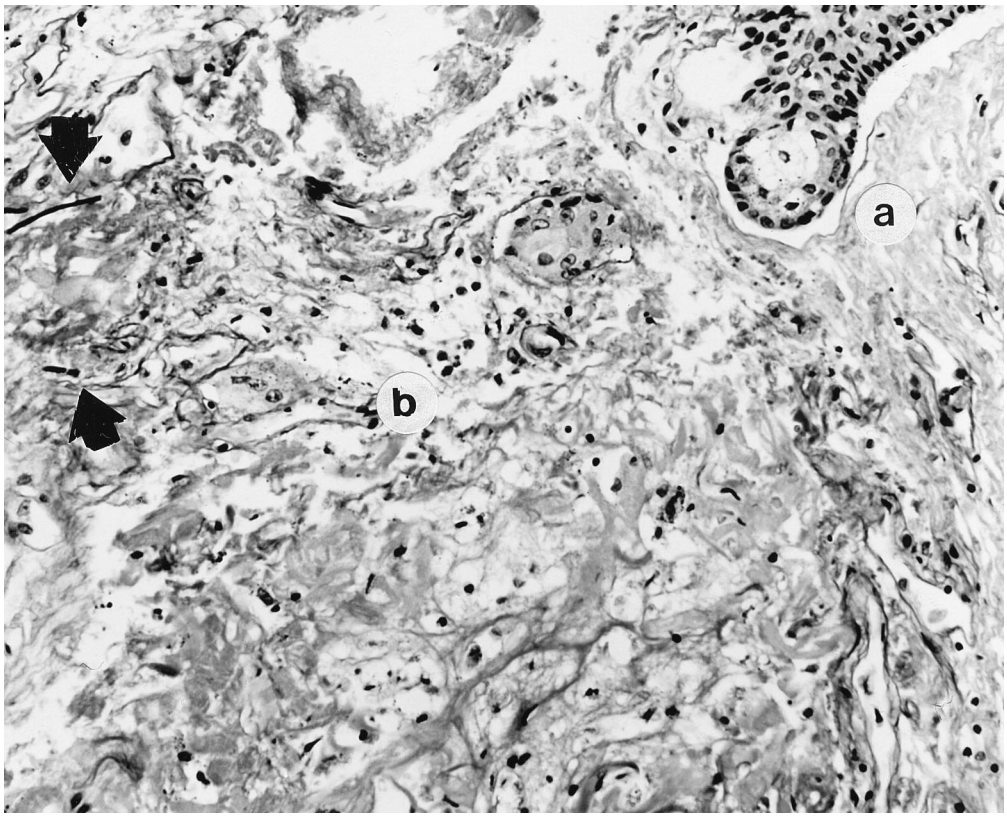

FIG. 1. Punch biopsy of skin stained with GMS shows that the surface epidermis is focally necrotic (a) and that the dermis has a sparse mononuclear infiltrate (b). Arrows point to short fragments of hyphae of *N. mangiferae*. Magnification, ×275.

photericin B and to at least some of the azoles, notably miconazole. Susceptibility to 5-FC, as judged by the MICs, was evident for the majority, but not all, of the isolates. Among the azoles taken internally, the MICs of both ketoconazole and itraconazole for most isolates indicated susceptibility. Examination of the MLCs, however, showed that the majority of isolates appeared to retain viability in the presence of most or all azoles, as well as 5-FC. They were, however, mainly susceptible to amphotericin B, although sometimes not strongly so. MICs for some isolates, most notably *S. hyalinum* R-1455, indicated strong resistance to all agents except amphotericin B. The single isolate of *S. lignicola* tested did not show significant differences in susceptibility from those of the other species tested.

DISCUSSION

Case patient. Factors which may have predisposed the present patient to *N. mangiferae* infection included his diabetes and chronic therapy with corticosteroids since both factors have been associated with other systemic fungal infections. Three previously reported deep infections with this organism involved diabetic patients (8, 39–41). One of these patients had a similar history of steroid use for chronic obstructive lung disease (39). For two other diabetic patients and a third patient receiving corticosteroid treatment for systemic lupus erythematosus, *N. mangiferae* was isolated from superficial infections without deeper invasion (5, 14, 62). This suggests that other host factors may also be important to allow for the development of deep tissue invasion. Our patient had very thin skin and at the time of his hospitalization was edematous. Whether these local factors resulted in any predisposition has not yet been clearly established.

Therapy. Optimal therapy of deep *Scytalidium* infections is not known. Therapy with amphotericin B has been effective in a patient with facial lesions and underlying immunosuppression (35–37) and in a French diabetic patient with dual infection of the maxillary sinus caused by a zygomycete and *N. mangiferae* (40, 41). The latter patient was treated initially with amphotericin and then ketoconazole over 3 months in response to the patient's renal dysfunction, but after a severe relapse, amphotericin B therapy was reinstated, with a good response. Dickinson et al. (8) used surgical drainage and debridement and 5-FC therapy over 2 months to treat a diabetic man with subcutaneous abscesses caused by *N. mangiferae* (referred to as *S. lignicola*, but see discussion below). Management of the underlying neutropenia combined with amphotericin B therapy was found to be effective in a child with fungemia and invasive abdominal lesions caused by *S. dimidiatum* (2). Therapy with ketoconazole has largely been ineffective, even though the organisms appear susceptible in vitro. In a brief mention of mycetoma caused by *N. mangiferae*, Drouhet and Dupont (9) suggested that treatment with ketoconazole appeared to be effective after 4 months, but relapse occurred after 1 year. Little improvement followed therapy for 10 months in a case of *N. mangiferae* infection (34) and for 6 months in a case of *S. hyalinum* infection (65). Aggressive treatment with intraocular amphothericin B, miconazole, and topical natamycin and surgical treatment failed to resolve an eye infection caused by *N. mangiferae* (1). Topical application of clotrimazole cream (Lotrimin; Schering) appeared to re-

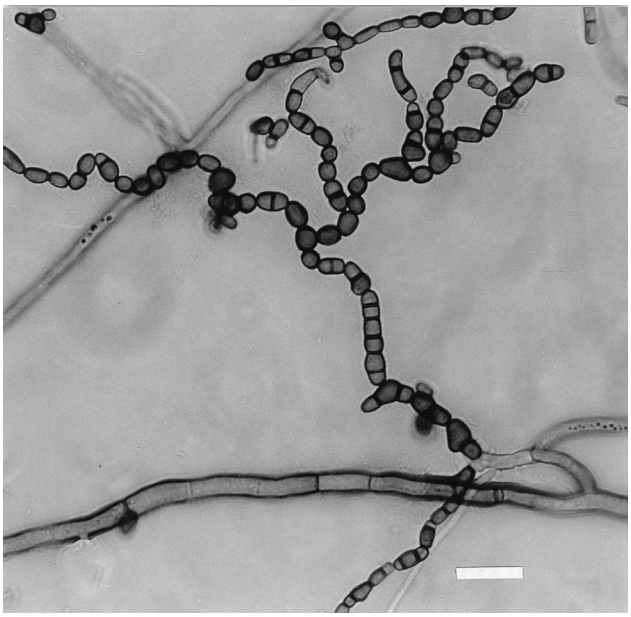

FIG. 2. *S. dimidiatum* synanamorph of *N. mangiferae* UAMH 6673. A slide culture preparation shows broad nonfragmenting hyphae and lateral branches fragmenting to form nonseptate or one-septate arthroconidia. Bar, 20 μm.

solve a soft tissue abscess in a diabetic male patient, but the patient reported several remissions over a 3-year period (39).

Our patient improved with combined therapy with systemic amphotericin B and topical application of clotrimazole cream. Subsequently, the clinical response seemed to correlate with stopping and later restarting therapy with the clotrimazole cream. The apparent beneficial effect of clotrimazole in this patient in combination with the in vitro effects of itraconazole provides some support for considering azoles as therapy. However, for patients in which therapy with azoles, mostly ketoconazole, has been used, clinical cures have not been achieved (1, 9, 34, 40, 41, 65).

Antifungal susceptibility. Susceptibility test results for a variety of isolates of *N. mangiferae* and *S. hyalinum* indicated

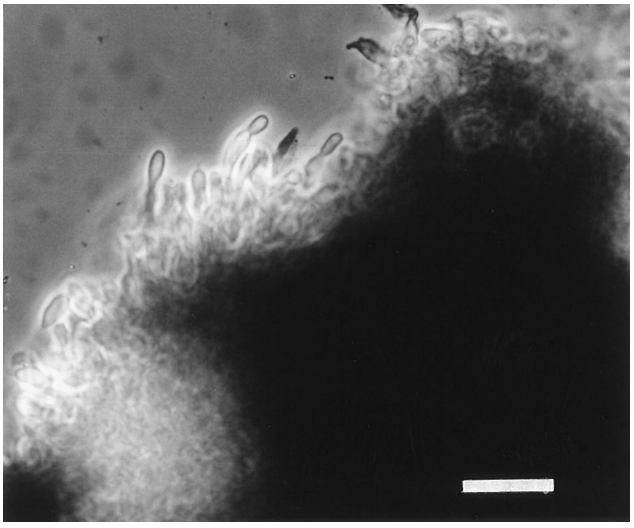

FIG. 3. Crushed pycnidium of *N. mangiferae* UAMH 6673 showing phialidic conidiogenous cells producing single-celled ellipsoidal conidia. Bar, 20 μm.

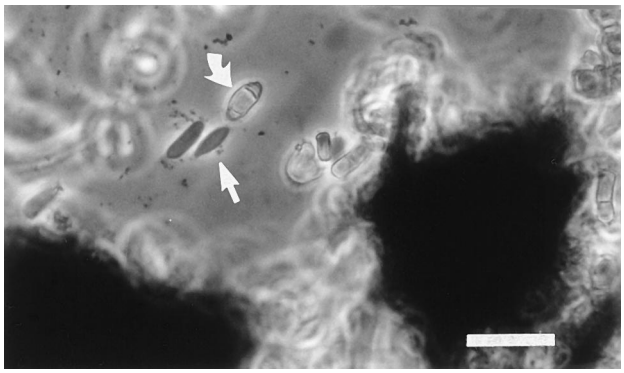

FIG. 4. Pycnidial conidia of *N. mangiferae* UAMH 6673. Shown are immature hyaline, single-celled conidia (straight arrow) and a mature pale brown conidium with median band (curved arrow). Bar, 20 μm.

relatively strong susceptibilities to amphotericin B and to ketoconazole, itraconazole, and miconazole. Although the MLCs of the azoles and 5-FC were less promising than the MICs, high MLCs alone may not necessarily indicate in vivo resistance. Direct lethality to the fungal inoculum may not always be necessary in an immunocompetent host, who may be able to eliminate fungal material incapacitated by merely fungistatic drug levels.

On the basis of only the MICs, our data were similar to in vitro susceptibility data reported for two isolates from patients with deep infections (8, 65) and data reported in the literature and reviewed by Moore (44). Dickinson et al. (8) stated that their isolate of *N. mangiferae* (reported as *S. lignicola*) was susceptible in vitro to 5-FC, amphotericin B, ketoconazole, and miconazole. They achieved clinical cure with surgery and 5-FC treatment. As our Table 1 shows, the apparent susceptibility of isolates of *N. mangiferae* to this drug, as judged by the MLCs, is very unusual, while apparent susceptibility of isolates, as judged by the MICs, is more common. The isolate of *S. hyalinum* examined by Zaatari et al. (65) showed moderate susceptibility to miconazole, as was found for some isolates in our study. Oyeka and Gugnani (48), using an agar dilution susceptibility testing method based on Emmons' modification of SDA, found that the MICs and MLCs of six topical azoles and fluconazole were low. Their highest fluconazole MICs and MLCs were 1 to 5 doubling dilutions lower than those seen in the present study, suggesting a strong effect connected with the test methodology used. While standardization has been achieved for susceptibility testing of some yeasts, there is no standard yet for testing mycelial fungi (10). Our study used SAAM-F for testing azoles, but RPMI 1640 (Sigma Chemical Co., St. Louis, Mo.) is now recommended because of commercial availability and good interlaboratory agreement in studies conducted with yeasts (49). However, these data indicate that results with SAAM-F and RPMI 1640 are essentially the same.

N. mangiferae and *S. hyalinum*, however, have a reputation for being very difficult to treat successfully not just when they are the cause of deep infections but also when they are the cause of cutaneous infections. Sporadic cures have been reported with clotrimazole (20), nail avulsion-ciclopirox olamine under occlusion (54), tioconazole (one of three patients only) (25), 10% boric acid in mineral oil (27), and apparently, Grow Strong nail hardener following clotrimazole therapy (one of three patients) (14). Ineffective results have been ascribed to ciclopirox olamine + glutaraldehyde (54), clotrimazole (14, 45), econazole (14), bifonazole (19), tioconazole (25), miconazole (14), ketoconazole (14, 22, 45), itraconazole (24), half-

TABLE 1. In vitro susceptibility of *N. mangiferae* and *S. hyalinum* to antifungal compounds

Species	Isolate no.[a]	48-h MIC (MLC) (μg/ml)[b]					
		AMB	5-FC	FLU	ITR	KETO	MON
N. mangiferae Form 1	UAMH 6673	≤0.29 (2.31)	ND (ND[c])	ND (ND)	0.3 (>10)	ND (ND)	ND (ND)
	R1058	≤0.14 (0.58)	20.2 (>322)	10 (>80)	0.3 (>10)	1.6 (>12.8)	≤0.6 (>20)
	R1059	≤0.14 (2.31)	≤10.1 (>322)	10 (>80)	0.3 (>10)	0.8 (>12.8)	≤0.6 (5)
	R1060	≤0.14 (2.31)	20.2 (322)	10 (>80)	0.6 (>10)	1.6 (>12.8)	≤0.6 (>20)
	R1061	≤0.14 (2.31)	20.2 (322)	5 (>80)	≤0.02 (>10)	0.1 (>12.8)	≤0.6 (20)
	R1062	≤0.14 (≤0.14)	40.3 (>322)	10 (>80)	2.5 (>10)	0.8 (>12.8)	≤0.6 (1.25)
	R1063	≤0.14 (1.16)	40.3 (>322)	20 (>80)	2.5 (>10)	3.2 (>12.8)	≤0.6 (>20)
	R1064	≤0.14 (2.31)	40.3 (>322)	5 (>80)	0.04 (10)	0.05 (6.4)	≤0.6 (2.5)
	R1065	0.29 (2.31)	161 (>322)	2.5 (80)	0.15 (5)	0.1 (1.6)	≤0.6 (1.25)
	R1456	≤0.14 (2.31)	80.7 (>322)	20 (>80)	>10 (>10)	6.4 (>12.8)	≤0.6 (>20)
	R1457	≤0.14 (4.62)	≤10.1 (>322)	10 (>80)	1.25 (>10)	0.8 (>12.8)	≤0.6 (>20)
Form 2	R1458	≤0.14 (0.29)	161 (>322)	10 (40)	0.6 (>10)	3.2 (12.8)	≤0.6 (2.5)
	R1459	≤0.14 (0.58)	161 (>322)	20 (80)	0.15 (10)	0.8 (6.4)	≤0.6 (1.25)
Form 3	R1460	≤0.14 (0.58)	≤10.1 (≤10.1)	ND (ND)	1.25 (>10)	3.2 (>12.8)	≤0.6 (10)
	R1461	≤0.14 (0.29)	≤10.1 (20.2)	40 (>80)	>10 (>10)	3.2 (>12.8)	≤0.6 (>20)
	R1066	≤0.14 (≤0.14)	≤10.1 (20.2)	20 (40)	≤0.02 (>10)	1.6 (>12.8)	≤0.6 (>20)
	R1067	≤0.14 (≤0.14)	≤10.1 (20.2)	10 (40)	≤0.02 (2.5)	1.6 (1.6)	≤0.6 (1.25)
S. hyalinum	R1455	≤0.14 (1.16)	80.7 (>322)	40 (>80)	1.25 (>10)	3.2 (>12.8)	≤0.6 (20)
	R1055	≤0.14 (≤0.14)	20.2 (80.7)	5 (80)	0.3 (0.3)	0.2 (0.2)	5 (5)
	R1056	≤0.14 (≤0.14)	≤10.1 (40.3)	5 (>80)	0.04 (0.6)	0.05 (1.6)	2.5 (10)
	R1057	≤0.14 (0.58)	40.3 (80.7)	2.5 (40)	0.04 (1.25)	0.05 (0.8)	≤0.6 (≤0.6)
S. lignicola	CBS 233.57	0.29 (1.16)	≤10.1 (>322)	20 (>80)	0.07 (1.25)	0.4 (6.4)	≤0.6 (2.5)

[a] UAMH, culture in University of Alberta Microfungus Collection and Herbarium; R, culture in University of Texas Health Science Center collection; CBS, culture obtained from Centraalbureau voor Schimmelcultures, Baarn, The Netherlands.
[b] Abbreviations: AMB, amphotericin B; 5-FC, flucytosine; FLU, fluconazole; ITR, itraconazole; KETO, ketoconazole; MON, miconazole.
[c] ND, test not done.

strength Whitfield's ointment (31), griseofulvin (19), and in one patient, a succession of various topical antifungal preparations (19). Further ineffective remedies mentioned in earlier literature on *N. mangiferae* and *S. hyalinum* infections are reviewed by Frankel and Rippon (14) and Moore (44).

The apparent discrepancy between in vitro results such as those presented in Table 1 and published in vivo results for infections with *N. mangiferae* and *S. hyalinum* may simply reflect current deficiencies in our general knowledge of how to apply in vitro antifungal test results to the clinical situation (15). Such deficiencies are especially pronounced when in vitro results contain ambiguities such as MICs indicating susceptibility juxtaposed with MLCs indicating resistance. More likely, however, this discrepancy also specifically reflects the complexity of treating fungi growing in the nail bed and keratinized skin, relatively hydrophobic environments much different than the liquid of the test tube. More experience with in vitro antifungal testing and treatments based on its predictions has been acquired with systemic fungal pathogens. Where atypical agents of cutaneous infection are concerned, successful prediction of the results of treatment may require considerable research as a subject in its own right.

Taxonomy and identifying features of human pathogenic *Scytalidium* species. Whenever a fungus is pleomorphic, disputes concerning classification may lead to unstable nomenclature. Both *N. mangiferae* and *S. lignicola* are pleoanamorphic fungi; i.e., they have more than one conidial type. Several factors have combined to make the situation complicated and a source of potential confusion. First, the name of the pycnidial morph was changed from *H. toruloidea* to *N. mangiferae*. Second, three cultural variants of *N. mangiferae* (forms 1 to 3) are recognized. One type (slow-growing form 3) is not known to produce pycnidia. Third, there are similarities both in morphology and in clinical presentation between *N. mangiferae* (form 1 type) and *S. hyalinum*, suggesting a close relationship between these species. Fourth, the *Scytalidium* synanamorph of *N. mangiferae* has been given the name *S. dimidiatum*, and some mycologists have considered *S. lignicola* to be a synonym. This has led to reports of infections caused by *S. lignicola*, but examination of those reports suggests that the fungal isolates involved are misidentified *N. mangiferae* isolates.

In their revision of *Hendersonula*, Sutton and Dyko (61) reduced the number of species from 30 to 3. Features characterizing *Hendersonula* included the lack of an associated synanamorph, a mycoparasitic habit, an eustromatic conidioma usually produced within host tissue, conidia of uniform pigmentation, and annellidic rather than phialidic conidiogenesis. Features that they recognized as important in defining the monotypic *Nattrassia* included uni- or multiloculate ostiolate pycnidia, conidiogenesis without proliferation of the conidiogenous cell (phialidic conidiogenesis), conidia which at maturity show median bands of darker color, and an arthroconidial synanamorph (Fig. 2 to 4). They found *Dothiorella mangiferae* H. & P. Sydow, described in 1916, to be the earliest name available and made the new combination *N. mangiferae.*

Isolates of *N. mangiferae* from either human or plant infected tissue are first recognized in the laboratory by the colonial and microscopic features of the arthroconidial

Scytalidium morph. Although Campbell (3) first reported differences in growth rates and production of pycnidia among isolates from humans, Moore (43, 44) has described three morphological variants which appear to correlate to the country of origin of the patient. Slightly fewer than half of all clinical isolates conform to the fast-growing type (form 1), which has features identical to those described for our isolate. The second largest group (form 3) occurs predominantly in individuals from the Indian subcontinent. It is distinguished by slow growth, scant aerial mycelium, grey rather than black colonies, absence of pycnidia, sparse or moderate production of arthroconidia, less variation in hyphal width, and abundance of hyphal loops. These nonpycnidial, slow-growing isolates have been putatively identified as *N. mangiferae* because of their characteristic hyphal ornamentation and isolation from patients with similar clinical conditions (4, 43, 44). Approximately 9% of isolates fall into a third, intermediate type (form 2) distinguished by slower-growing colonies demonstrating broad concentric zones.

Because pycnidia may be difficult to express or may be absent, as in form 3 isolates, it has been considered useful to apply a name to the arthroconidial state. Sigler and Carmichael (57) proposed that a cross-reference name, the *Scytalidium* syanamorph of *N. mangiferae*, be used for the arthroconidial morph. While clearly indicating the link between the two morphs, cross-reference names are cumbersome, and others have preferred to use a separate Linnaean binomial for reporting purposes. Sutton and Dyko (61) took up the name *Torula dimidiata* Penzig 1882 as *S. dimidiatum* (Penz.) Sutton & Dyko, but it is unclear whether they based their decision on the original description or on examination of type material. Although Fawcett (12) had used *T. dimidiata* for isolates from frost-damaged citrus trees in California, Wilson (64) decided to abandon this name because he considered Penzig's description inadequate to make an accurate comparison. Since *T. dimidiata* has not been described by a recent author, it would have been helpful if Sutton and Dyko (61) had provided an illustration of the type specimen. It may be questioned whether a separate Linnaean binomial is needed in this case, especially if the typification of *T. dimidiata* is uncertain. Despite these concerns, the name *S. dimidiatum* is being used by many mycologists because of the difficulties in inducing the pycnidial morph.

Sutton and Dyko (61) also placed *S. lignicola*, the type species of *Scytalidium*, into synonymy with *S. dimidiatum*, but others have disagreed with this decision (29, 44, 58, 59). *S. lignicola* is distinguished by the hyaline, uniformly narrow (2.5 μm or less in width), usually unbranched, fertile hyphae arising as lateral branches from the vegetative mycelium. The hyaline cylindrical arthroconidia, termed "conidia vera" by Pesante (49), are accompanied by swollen intercalary or terminal chains of chlamydospores which are initially hyaline and which gradually become brown. Although usually indehiscent, the chlamydospores may fracture from the thin-walled supporting hypha during the preparation of tease mounts. As the chlamydospores develop and become melanized, the colonies darken from off-white to yellowish grey, grey, or black, depending on their abundance. Their development can be influenced by medium, forming less abundantly on phytone yeast extract agar (BBL) than on Pablum cereal agar (27). Most isolates also produce a strong yellow, diffusible pigment. The microscopic and colonial features of *S. lignicola* have been illustrated in several recent publications (44, 57, 59, 63) and are not repeated here.

Compared with the uniformly narrow, cylindrical arthroconidia of *S. lignicola*, the arthroconidia of the form 1 type of *N. mangiferae* are more variable in width and color. Arthroconidia are formed by fragmentation of both narrow and broad hyphae and measure from 2.5 to 10 μm, sometimes rounding up to 10 to 16 μm (43, 44, 57, 59). Narrower arthroconidia tend to be hyaline or subhyaline, and broader arthroconidia are dark brown with strongly refractile septa (Fig. 3). Some of the broad vegetative hyphae do not form arthroconidia, and they may be surrounded by brown slime.

S. hyalinum Campbell & Mulder (6) also forms arthroconidia which are often thick walled and variable in width, but they remain hyaline or subhyaline. It causes superficial infections remarkably similar in clinical features to those caused by *N. mangiferae*, and occurrences of mixed infections have been reported (42). Similarities in clinical condition, arthroconidium development, and sterol content (26) and the demonstration of antigenic cross-reactions (46) suggest that these species are closely related (43, 44) and should not be placed in separate genera on the basis of color, as has been proposed (55). Use of the name *S. hyalinum* for the synanamorph of *N. mangiferae* (32) is incorrect since no direct relationship between them has been proven and *S. dimidiatum* is an earlier name. Results of isoenzyme studies corroborated a close relationship between these species, but demonstrated differences between them and *S. lignicola* (33).

Ecology and distribution. The natural habitat of *S. hyalinum* is not yet known, but most cases of infection have occurred in individuals from the Caribbean or West Africa (6, 23, 43, 44). One exception is the case of deep infection in a resident of the United States discussed below. In nature, *N. mangiferae* is known as a wound-invading pathogen of a variety of woody hosts in tropical and subtropical countries worldwide (52, 61). Although it has been reported from many hosts in the United States, including *Arbutus*, *Ficus*, *Citrus*, *Juglans*, and others, its distribution is restricted in more temperate climates such as Canada, where it has been reported only from southwest British Columbia (11, 18). In Arizona, the state in which the patient described here resides, *N. mangiferae* is known to infect citrus trees. Moreover, a recent report documented the first North American incidence of dieback in *Eucalyptus camaldulensis* trees in southwestern Arizona (38). In North America, *S. lignicola* has been shown to be one of the commonest fungi causing soft rot of utility poles (63). It also occurs on conifers and some hardwood species, causing staining (11, 18, 57).

Critical review of published reports of deep infection due to *N. mangiferae*, *S. hyalinum*, and *S. lignicola*. To date, 10 cases of deep infection attributed to *N. mangiferae*, *S. hyalinum*, and *S. lignicola* have been described. On the basis of our review of those reports and in some cases reexamination of the isolates themselves, we conclude that *S. lignicola* has not been documented as the cause of human infection.

Three patients, like ours, were diabetic. Dickinson et al. (8) described multiple subcutaneous abscesses of the left foot in a diabetic male patient with hypertension. The isolate from that patient (NCMH 1255 = ATCC 52538 = UAMH 4755), originally identified as *S. lignicola*, was found to produce pycnidia typical of *N. mangiferae* (58). Histopathological findings for the isolate from that patient revealed branched dematiaceous hyphae. Nonpigmented, refractile, and often sinuous hyphae are the most common histopathological finding in *N. mangiferae* infections, but pigmented hyphae may also be found (44). *N. mangiferae* caused similar subcutaneous lesions in the ankle area of a diabetic male patient with a long-term history of steroid use for chronic obstructive lung disease (39). The isolate from that patient failed to produce pycnidia, but was otherwise typical of *N. mangiferae*. A third diabetic patient who was a wood-carver had an infection of the maxillary sinus

caused by *N. mangiferae* as well as a zygomycete (41). Later, Miegeville (40) was able to isolate *N. mangiferae* from a sample of wood used by the patient prior to the onset of infection.

Wood may also have been the source of infection caused by *N. mangiferae* in a patient with a history of arthritis and posttraumatic stress disorder who hit the web between thumb and finger with a wooden mallett (34). Similarly, the fungus may have been implanted directly into the eye by a thorn in a patient with endophthalmitis (1). Direct inoculation was also likely the cause of mycetoma in a West Indian man, but the infection was mentioned only incidentally by Drouhet and Dupont (9).

Immunosuppression has been the underlying condition predisposing three patients to deep infection. *N. mangiferae* was the cause of verrucose facial lesions and accompanying onychomycosis in an Algerian man (35) and of fungemia and abdominal lesions in an adolescent Moroccan boy (2). Unusual findings in the latter case were the recovery of the fungus from a culture of blood and the failure to isolate it from necrotic lesions on two toes. The isolate from the Algerian patient demonstrated features consistent with *N. mangiferae*, but it failed to produce pycnidia (UAMH 6569 = IP 1093). *S. hyalinum* was identified as the cause of multiple subcutaneous left-foot cysts in an immunocompromised patient (UAMH 4760) (65). While this patient's toenails and left thumbnail were thick, yellow, and focally brown and the skin of the great toe was thickened, features consistent with clinical cutaneous *S. hyalinum* infection, mycological investigation of these sites was apparently not undertaken.

S. lignicola was identified as the etiologic agent causing erythematous lesions on the upper lip of a male heavy equipment mechanic with tuberculosis (51). However, the description provided by the authors of hyphae and arthroconidia which vary greatly in width and have thick walls is consistent with the features of *N. mangiferae*/*S. dimidiatum.*

The difficulties in nomenclature of the organisms encountered in the cases of deep infections described above has been evident in infections of the skin and nails as well. Three cases of nail and toeweb infections in Brazil were attributed to *S. lignicola* (7, 13). The authors cited both *S. lignicola* and *S. hyalinum* as synanamorphs of *N. mangiferae*, demonstrating the apparent confusion surrounding the use of these names. In our hands, one of their isolates, kindly provided by A. R. Costa, formed pycnidial conidia typical of *N. mangiferae* (UAMH 6804).

It is not yet known whether this rather low incidence of deep infection results from a poor invasive capacity of these fungi, failure to isolate the pathogens due to susceptibility to cycloheximide incorporated into some routine fungal culture media, or inadequate identification. On the basis of our review, we conclude that only *N. mangiferae*, inclusive of its *Scytalidium* synanamorph (*S. dimidiatum*), and *S. hyalinum* have been conclusively shown to cause infections in humans. It is our contention that *S. lignicola* should be considered a distinct species and that its ability to cause disease in humans has not yet been demonstrated.

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