Onychomycosis caused by nondermatophytic molds: Clinical features and response to treatment of 59 cases

Antonella Tosti, MD, Bianca Maria Piraccini, MD, and Sandra Lorenzi, MD *Bologna, Italy*

Background: Nail invasion by nondermatophytic molds (NDM) is considered uncommon with prevalence rates ranging from 1.45% to 17.6%.

Objective: We report the clinical features and response to treatment of onychomycosis caused by these molds.

Methods: From 1995 through 1998 we performed a mycologic study on 1548 patients affected by nail disorders, and we diagnosed 431 cases of onychomycosis including 59 cases of onychomycosis caused by molds. These include 17 patients with onychomycosis caused by *Scopulariopsis brevicaulis*, 26 patients with onychomycosis caused by *Fusarium* sp, 9 patients with onychomycosis caused by *Acremonium* sp, and 7 patients with onychomycosis caused by *Aspergillus* sp.

Results: Onychomycosis caused by *S brevicaulis*, *Fusarium* sp, and *Aspergillus* sp may often be suspected by clinical examination. In fact 38 of 50 patients with onychomycosis resulting from these molds were affected by proximal subungual onychomycosis associated with inflammation of the proximal nailfold. In our experience mold onychomycosis is not significantly associated with systemic diseases or immunodepression. NDM are difficult to eradicate; by using and combining different treatments (systemic itraconazole, systemic terbinafine, topical terbinafine after nail plate avulsion, and ciclopirox nail lacquer) we were able to cure only 69.2% of patients with *S brevicaulis* onychomycosis, 71.4% of patients with *Acremonium* onychomycosis, and 40% of patients with *Fusarium* onychomycosis. *Aspergillus* onychomycosis, on the other hand, responded very well to therapy and all our patients were cured after systemic or topical treatment. Eradication of the mold produced a complete cure of the nail abnormalities in all the patients who responded to treatment.

Conclusion: Clinical examination usually suggests diagnosis of onychomycosis resulting from NDM. Topical treatment can be more successful than systemic therapy to cure onychomycosis caused by *S brevicaulis*, *Fusarium* sp, and *Acremonium* sp. (J Am Acad Dermatol 2000;42:217-24.)

Nondermatophytic molds (NDM) are filamentous fungi that are commonly found in nature as soil saprophytes and plant pathogens. Nail invasion by NDM is considered uncommon with prevalence rates ranging from 1.45% to 17.6%.[1-3] This variation may reflect (1) geographic differences in mold distribution, (2) differences in the criteria used for diagnosing mold onychomycosis, and (3) use of mycologic methods inappropriate for mold growth.

From the Department of Dermatology, University of Bologna.
Accepted for publication Aug 30, 1999.
Reprint requests: Antonella Tosti, MD, Department of Dermatology, University of Bologna, Via Massarenti, 1, 40138 Bologna, Italy.
Copyright © 2000 by the American Academy of Dermatology, Inc.
0190-9622/2000/$12.00 + 0 **16/1/102646**

Although the list of NDM that have occasionally been isolated from nails is quite long,[1] only a few species of molds are regularly identified as causing onychomycosis. These include *Scopulariopsis brevicaulis*, *Fusarium* sp, *Acremonium* and *Aspergillus* sp, *Scytalidium* sp, and *Onychocola canadiensis*.[4-9]

From 1995 to 1998 we performed a mycologic study on 1548 patients affected by nail disorders, and we diagnosed 59 cases of onychomycosis caused by molds. These include 17 patients with *S brevicaulis* infection, 26 with *Fusarium* sp, 9 with *Acremonium* sp, and 7 with *Aspergillus* sp. Seven of these patients had been previously reported elsewhere.[10-12]

The aim of this article is to report the clinical features and response to treatment of onychomycosis caused by these molds.

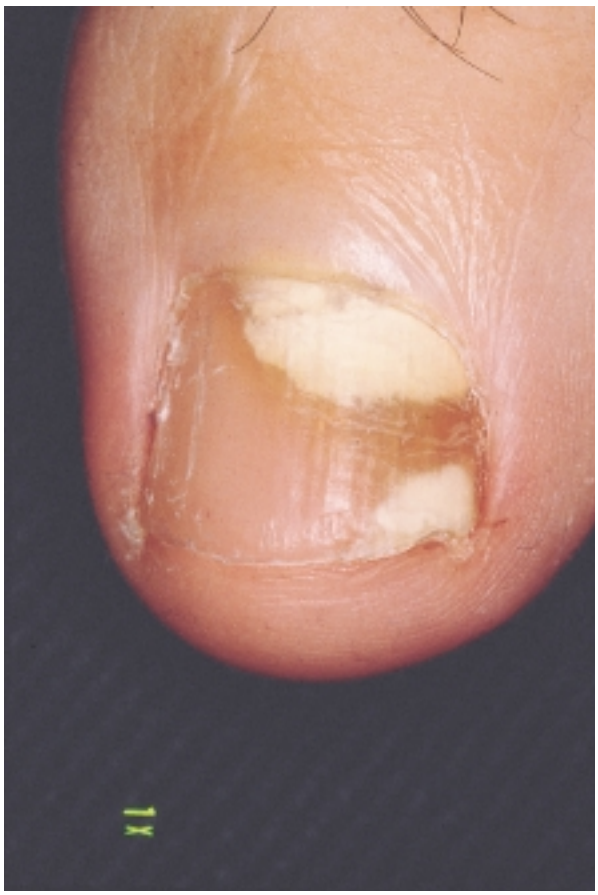

Fig 1. Proximal subungual onychomycosis caused by *Scopulariopsis brevicaulis* of left great toenail.

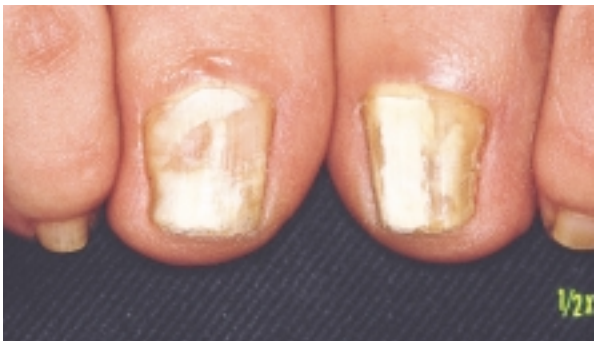

Fig. 2

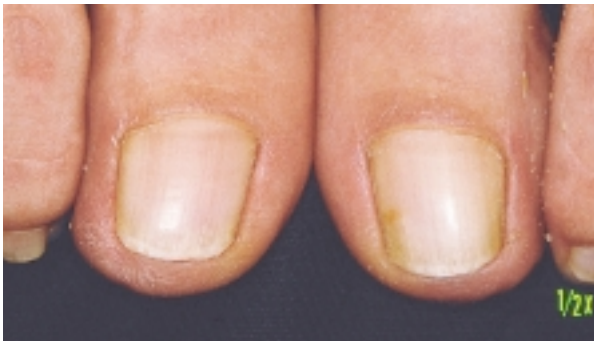

Fig. 3

Figs 2 and **3.** Proximal subungual onychomycosis of great toenails caused by *Scopulariopsis brevicaulis* before **(Fig 2)** and after **(Fig 3)** 4 months of treatment with pulse itraconazole 400 mg/day for 1 week a month.

Table I. Fungi responsible for onychomycosis diagnosed at the Department of Dermatology of the University of Bologna in the years 1995-1998

Year	No. of isolated fungi	Dermatophytes	*T rubrum*	*T interdigitale*	*E floccosum*	Molds	*S brevicaulis*	*Fusarium*	*Acremonium*	*Aspergillus*
1995	112	107	94	11	2	5	2	1	1	1
1996	93	83	56	25	2	10	6	2	2	—
1997	117	99	68	31	—	18	3	8	3	4
1998	109	83	60	20	3	26	6	15	3	2
Total	431	372	278*	87†	7	59	17	26	9	7

*Including 6 mixed infections (*T rubrum* + *Scopulariopsis brevicaulis*).
†Including 2 mixed infections (*T interdigitale* + *Scopulariopsis brevicaulis*).

PATIENTS AND METHODS

Patients

From 1995 to 1998 we performed nail mycology on 1548 patients with nail abnormalities. These 1548 patients came from two sources: patients referred by general practitioners or dermatologists to our Nail Mycology Laboratory Service, or patients examined at our Outpatient Consultation for Nail Disorders. In both cases we personally inspected the nail signs and made a presumptive clinical diagnosis before taking the samples for mycology. When the results of mycology did not confirm our presumptive diagno-

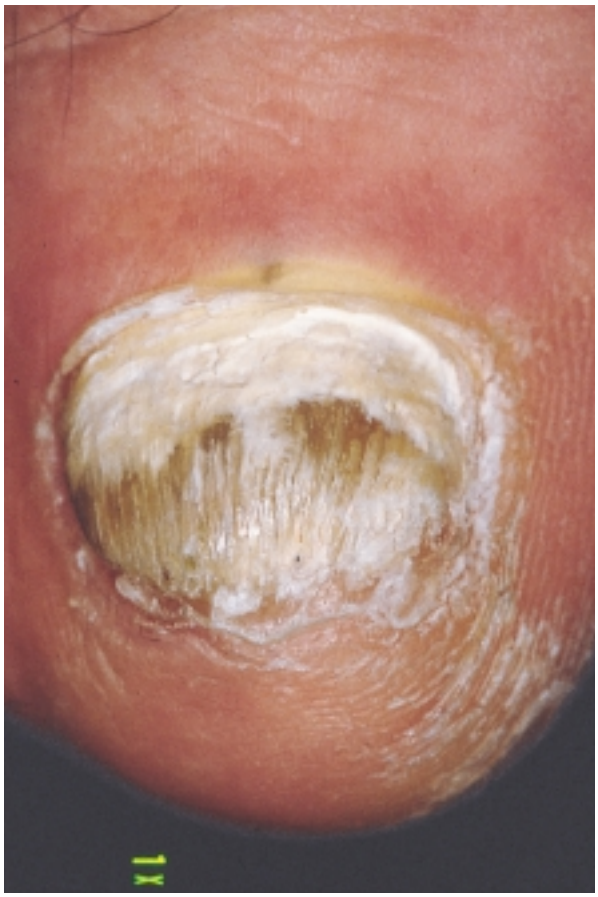

Fig 4. Proximal subungual onychomycosis of left great toenail caused by *Fusarium oxysporum*. Note marked periungual inflammation.

sis, we always re-examined the patient and took additional samples for mycology.

Methods

In patients with distal subungual onychomycosis (DSO), nail samples were obtained from the most proximal portion of the affected nail by scraping the hyperkeratotic nail bed. In proximal subungual onychomycosis (PSO) we used an electric drill to perforate the superficial nail and obtained the sample by scraping the exposed nail plate with a disposable scalpel. Nail samples were microscopically studied after clearing for 3 hours in 40% potassium hydroxide (KOH). For cultures, nail fragments were inoculated in Sabouraud-agar chloramphenicol medium, with and without cycloheximide, and incubated at 27°C for 3 weeks. Twenty inocules were performed in each plate. Lactophenol cotton-blue mounts of the colonies were used for identification of the cultures.

Diagnosis of NDM onychomycosis was made on the basis of the following criteria: (1) nail abnormalities consistent with this diagnosis; (2) positive KOH preparation with presence of hyphae in the nail keratin; (3) failure to isolate a dermatophyte in culture; and (4) growth of more than 5 colonies of the same mold in at least 2 consecutive nail samplings.

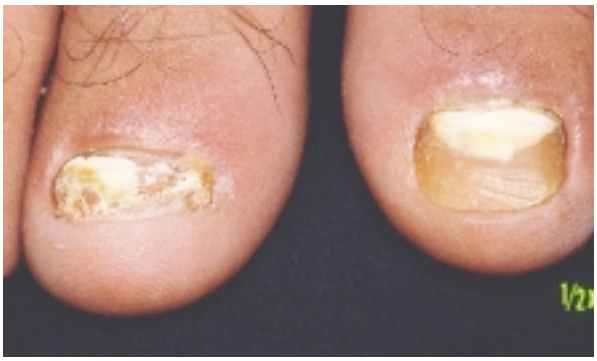

Fig 5. Proximal subungual onychomycosis of great toenails caused by *Fusarium oxysporum*.

Treatment

Patients who accepted treatment at our department were examined every 2 months until mycologic and clinical cure. In patients with NDM onychomycosis diagnosed before 1998, we always used systemic antifungals as first treatment. Itraconazole 400 mg daily for 1 week a month was given to 21 patients, and terbinafine 250 mg daily for 4 months was prescribed to 6 patients. Treatment was continued for 2 months in fingernail infection and for 4 months in toenail infection.

In 1998 we started to use topical antifungals as first-choice treatment for NDM onychomycosis. We prescribed 8% ciclopirox nail lacquer to be applied daily in 12 patients and topical terbinafine after chemical avulsion of the nail plate with 40% urea ointment in 6 patients. Topical treatment was prolonged for 8 to 12 months.

RESULTS

Our results are reported in Table I. A diagnosis of onychomycosis was established in 431 of the 1548 patients who submitted to nail mycology (27.8%). NDM were responsible for 59 cases, which represent 13.6% of all the onychomycosis diagnosed in the considered period. In 9 additional cases a mold (always *S brevicaulis*) was isolated together with *Trichophyton rubrum* (7 cases) or *T interdigitale* (2 cases) in repeated cultures. All patients with mold onychomycosis were white. Molds actually grew in 129 nail samples, but in 61 cases they were considered nail contaminants because their presence was

Table II. Clinical features and response to treatment of our series of patients with onychomycosis caused by nondermatophytic molds

	M/F	Age range (y) (mean)	FN/TN	DSO/PSO/WSO	Periungual inflammation	Immunodepression
S brevicaulis	5/12	20-81 (53.9)	-/16	7/10/-	10	1*
Fusarium sp¶	7/19	20-79 (47.5)	5/21	5/21/-	27	1#
Acremonium sp	4/5	34-69 (48)	-/9	9/-/-	—	—
Aspergillus sp	5/2	41-73 (60)	1/6	-/7/-	7	—

DSO, Distal subungual onychomycosis; *FN,* fingernails; *IDDM,* insulin-dependent diabetes mellitus; *PSO,* proximal subungual onychomycosis; *TN,* toenails; *WSO,* white superficial onychomycosis.
*Common variable immunodeficiency.
†One patient previously unsuccessfully treated with ciclopirox.
‡One patient previously unsuccessfully treated with pulse itraconazole.
§One patient previously unsuccessfully treated with amorolfine.
||Some patients underwent more than 1 treatment.
¶Ten patients younger than 40 years.
#AIDS.

not confirmed by repetitive isolation or the clinical examination was not consistent with a diagnosis of onychomycosis. The frequency of NDM onychomycosis increased almost 4-fold during the 4-year period. This especially resulted from a great increase in the number of cases of *Fusarium* sp infection.

Seventeen patients were affected by onychomycosis caused by *S brevicaulis*. *S brevicaulis* onychomycosis always affected toenails, involving a maximum of 2 nails, mostly the great toenails. In one patient it was associated with tinea pedis resulting from *S brevicaulis*. Ten patients with *S brevicaulis* infection had a PSO characterized by a white, yellow, or orange discoloration of the nail plate (Fig 1), often involving the entire length of the nail. The anamnesis always revealed that the nail signs first involved the lunula region and then spread to involve the distal nail. Periungual inflammation was frequently observed, and 7 patients had been previously treated with antibiotics or anti-inflammatory drugs for their painful periungual inflammation. Duration of the nail abnormalities before our examination ranged from 1 month to 12 years (mean, 2 years). Four patients described a very rapid spread of the onychomycosis since the appearance of the first signs.

Treatment with systemic or topical antifungals was prescribed in 13 patients, but only 9 of them were eventually cured (69.2%) (Table II) (Figs 2 and 3).

Fusarium onychomycosis was diagnosed in 26 patients. *F solani* was responsible for 8 cases and *F oxysporum* for 18 cases. A total of 21 patients presented a PSO associated with painful periungual inflammation. The affected nail was yellow-white and often showed an opaque surface. The proximal nailfold and the cuticle often appeared yellow-white, indicating the proximal origin of the infection (Figs 4-6). In some cases the distal nail showed a white discoloration caused by distal progression (Fig 7). Some patients complained of periodic inflammatory flares with purulent discharge.

Duration of *Fusarium* onychomycosis ranged from 1 month to 15 years (mean, 3 years). Only 8 of the 20 patients with *Fusarium* infection who underwent treatment were eventually cured (40%) (Figs 7 and 8).

Onychomycosis caused by *Acremonium* sp was diagnosed in 9 patients. Clinically, the affected nail usually showed one or a few longitudinal white streaks extending from the distal margin to the proximal nail plate. Onychomycosis was asymptomatic in all cases. Duration of *Acremonium* onychomycosis ranged from 2 months to 4 years (mean, 16 months).

Aspergillus onychomycosis was diagnosed in 7 patients. *A niger* was responsible for 3 cases, *A flavus* for 3, and *A terreus* for 1. All patients presented a PSO associated with marked painful inflammation of the periungual tissues. The affected nail showed a diffuse milky-white discoloration that involved the whole length of the nail plate. In 1 patient the entire nail thickness was involved, resulting in marked friability of the nail surface. All 3 nails affected by *A niger* onychomycosis showed a black discoloration of the lunula. In one patient this was associated with purulent discharge from the proximal nailfold. Onychomycosis caused by *Aspergillus* sp was cured in all 5 patients who accepted treatment (Figs 9 and 10).

Associated diseases	Previous nail disease	Patients cured/patients not cured				Patients cured/patients treated
		Pulse itraconazole 400 mg	Terbinafine 250 mg	Ciclopirox nail lacquer	Nail avulsion + topical terbinafine	
—	1 (psoriasis)	2†/4	1/0	5‡/1	1‡/2§	9/13‖
1 Raynaud phenomenon	3 (trauma)	3/10	2‡/2†	3/0	0/2	8/20‖
1 IDDM	1 (trauma)	0/3	1/1†§	2‡/1	2‡/0	5/7‖
—	2 (1 LP, 1 psoriasis)	1†/0	2/0	1/1	1/0	5/5‖

DISCUSSION

In the past few years we have diagnosed a rather high number of cases of onychomycosis caused by NDM, particularly *Fusarium* sp, in our department. In all our patients NDM produced nail abnormalities that were clinically consistent with a diagnosis of onychomycosis, in most cases PSO. Our experiences are unique because we have our own mycology laboratory and we do not process nail samples if we do not see the patient and personally take the sample. The occurrence of 26 cases of *Fusarium* nail infection in 4 years is really noticeable, and our data, together with the results of other mycologic laboratories in Italy,[13,14] suggest that this mold is becoming a relatively common pathogen in our country.

Onychomycosis caused by *S brevicaulis*, *Fusarium* sp, and *Aspergillus* sp may often be suspected by clinical examination. In fact, 38 of 50 patients with onychomycosis caused by these molds were affected by PSO associated with inflammation of the proximal nailfold. PSO may be limited to the lunula region or affect the whole nail plate. Fungal invasion of the proximal nailfold is often visible through the cuticle as a whitish-yellow discoloration. Periungual inflammation may be quite marked and painful and in some cases associated with purulent discharge; patients are frequently misdiagnosed as having a bacterial infection.

Periungual inflammation was not only observed in patients with PSO, but was also seen in 5 patients with DSO caused by *Fusarium* sp. The presence of inflammation, therefore, should strongly suggest a mold onychomycosis, this feature being, at least in our experience, almost never seen in onychomycosis caused by dermatophytes. *Acremonium* onychomycosis, on the other hand, is not associated with characteristic clinical features, and all our patients presented a DSO that was indistinguishable from a dermatophyte onychomycosis.

The mycologic diagnosis of onychomycosis in our patients was always easy because molds were clearly visible at direct microscopy, which in the cases of *S brevicaulis* and *Aspergillus* sp also suggested the diagnosis, and grew very easily in the Sabouraud's agar chloramphenicol medium. In most of our cases mold isolation was confirmed by more than 2 nail samplings, because the 45 patients who were treated at our department underwent clinical and mycologic examination every 2 months and in most of them (n = 26) the infection persisted for several months despite treatment.

Treatment of onychomycosis caused by nondermatophytic molds is still not well standardized, and several authors underline the fact that NDM onychomycosis frequently does not respond to systemic antifungals.[4,15] Our data confirm that nondermatophytic molds are difficult to eradicate. In fact, using and combining different treatments, we were able to cure only 69.2% of patients with *S brevicaulis* onychomycosis, 71.4% of patients with *Acremonium* onychomycosis, and 40% of patients with *Fusarium* onychomycosis. Although itraconazole has recently been reported to be effective in nail infections caused by *Aspergillus* sp, *Fusarium* sp, and *S brevicaulis* with a mycologic and clinical cure rate of 88% (15 of 17 patients),[16] our experience with this drug

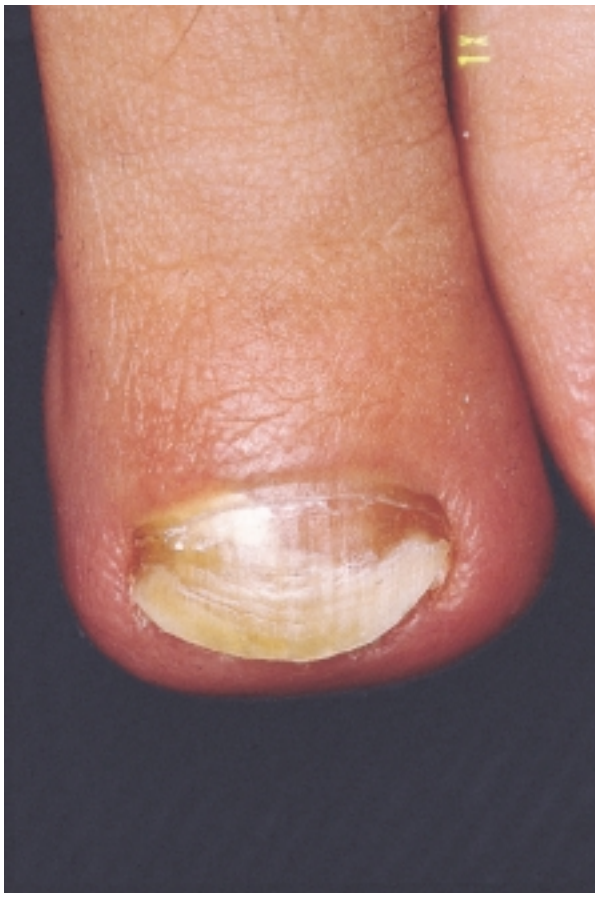

Fig 6. Proximal subungual onychomycosis of 2nd right toenail caused by *Fusarium solani*.

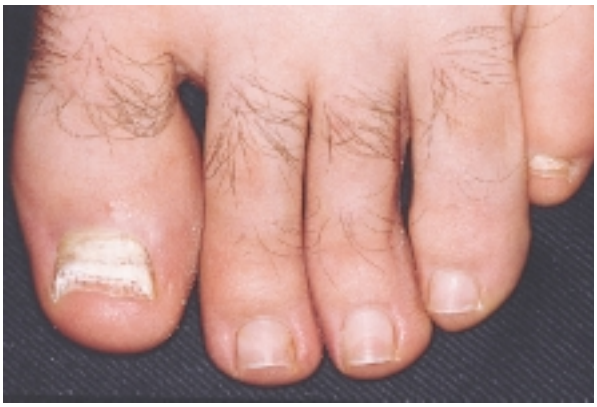

Fig. 7

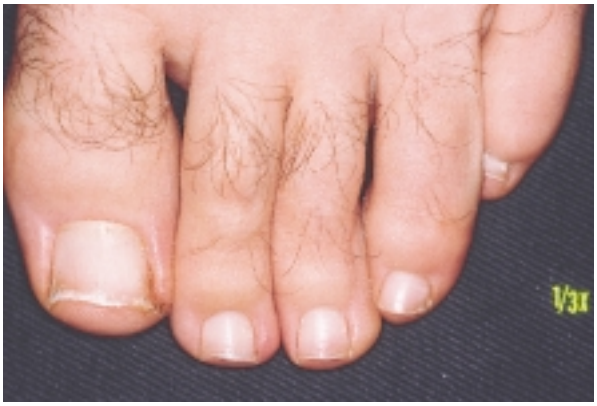

Fig. 8

Figs 7 and **8.** Proximal subungual onychomycosis of left great toe caused by *Fusarium oxysporum* before **(Fig 7)** and after **(Fig 8)** 12 months of treatment with ciclopirox nail lacquer.

was not as successful. In fact, except for *Aspergillus* sp, NDM onychomycoses scarcely responded to systemic antifungals, and with use of terbinafine or itraconazole we were able to cure only 42.8% of patients with *S brevicaulis* onychomycosis, 20% of patients with *Acremonium* onychomycosis, and 29.4% of patients with *Fusarium* infection. Our experience is based on a limited number of patients and does not permit us to compare the efficacy of different drugs. However, terbinafine and itraconazole were often both ineffective. We obtained better results with topical than with systemic drugs, and 8% ciclopirox nail lacquer or topical terbinafine after nail avulsion cured 11 of the 16 patients with onychomycosis caused by *S brevicaulis*, *Fusarium* sp, or *Acremonium* sp who received this treatment. *Aspergillus* onychomycosis, on the other hand, responded very well to therapy, and all our patients were cured after systemic or topical treatment. Eradication of the mold produced a complete cure of the nail abnormalities in all the patients who responded to treatment. This observation not only confirms mold pathogenicity, but also indicates that NDM, like dermatophytes, can invade healthy nails and that local factors are not important for the occurrence of this type of onychomycosis. Although secondary colonization of a dystrophic nail by molds is common,[17] only 9 of our patients complained of nail abnormalities before the onset of the onychomycosis. None of them, however, had abnormally thickened toenails, where molds can be frequently isolated. We did not include in this series nails with onychogryphosis or pachyonychia that harbored a mold because mold isolation in these cases was considered a secondary phenomenon.

In our experience mold onychomycosis is not significantly associated with systemic diseases and should not be considered a sign of immunodeficiency because only 2 of our patients were affected by immunodeficiency, including an HIV-infected patient

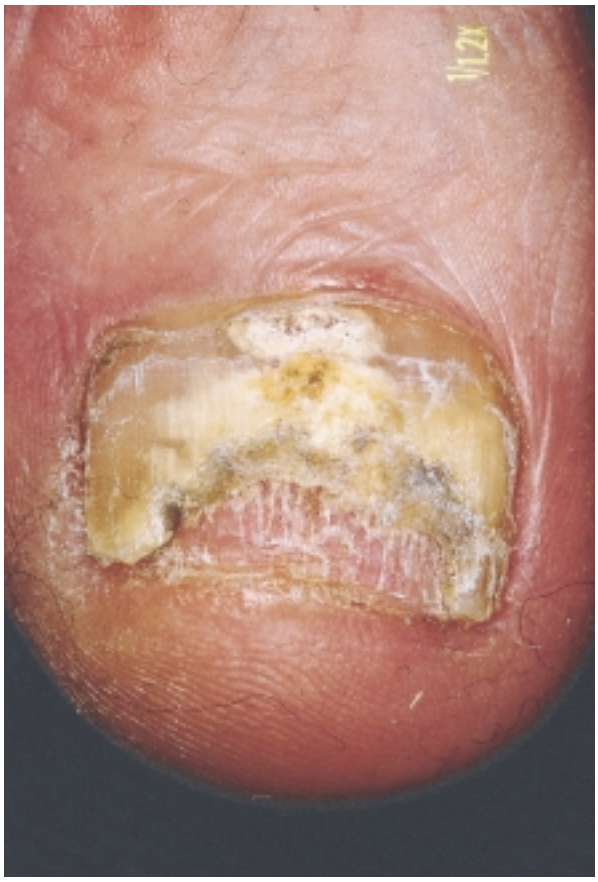

Fig. 9

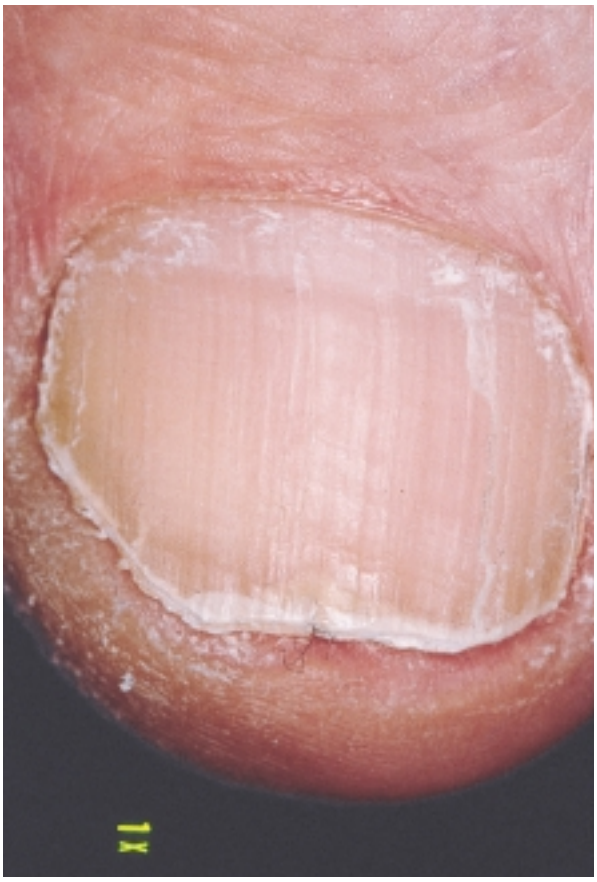

Fig. 10

Figs 9 and **10.** Proximal subungual onychomycosis of left great toe caused by *Aspergillus terreus* before **(Fig 9)** and after **(Fig 10)** 4 months of treatment with pulse itraconazole 400 mg/day for 1 week a month.

who died of a *Fusarium* infection that probably originated from the nail infection. This case, however, confirms that *Fusarium* onychomycosis should be considered a very serious disease in immunocompromised patients.[18-20]

We have never isolated *Scytalidium* sp in our department and to our knowledge this mold, which is not uncommon in North Europe, Canada, and the United States,[7] has never been isolated in Italy.

REFERENCES

1. Haneke E. Fungal infections of the nail. Semin Dermatol 1991;10:41-53.
2. Zaias N. Onychomycosis. Arch Dermatol 1972;105:263-74.
3. Kenna ME, Elewski BE. A US epidemiological survey of superficial fungal diseases. J Am Acad Dermatol 1996;35:539-42.
4. Denning DW, Evans EGV, Kibbler CC, Richardson MD, Roberts MM, Rogers TR, et al. Fungal nail diseases: a guide to good practice (report of a working group of the British society for medical mycology). Br Med J 1995;311:1277-81.
5. Campbell CK, Johnson EM, Warnock DW. Nail infection caused by *Onychocola canadiensis*: report of the first four British cases. J Med Vet Mycol 1997;35:423-5.
6. Gupta AK, Horgan-Bell CB, Summerbell RC. Onychomycosis associated with *Onychocola canadiensis*: ten case reports and a review of the literature. J Am Acad Dermatol 1998;39:410-7.
7. Gupta AK, Elewski BE. Nondermatophyte causes of onychomycosis and superficial mycoses. Curr Top Med Mycol 1996;7:87-97.
8. Rush-Munro FM, Black H, Dingley JM. Onychomycosis caused by *Fusarium oxysporum*. Australas J Dermatol 1971;12:18-29.
9. Summerbell RC, Kane J, Krajden S. Onychomycosis, tinea pedis and tinea manuum caused by non-dermatophytic filamentous fungi. Mycoses 1989;32:609-19.
10. Tosti A, Piraccini BM, Stinchi C, Lorenzi S. Onychomycosis due to *Scopulariopsis brevicaulis*: clinical features and response to systemic antifungals. Br J Dermatol 1996;135:799-802.
11. Baran R, Tosti A, Piraccini BM. Uncommon clinical features of *Fusarium* nail infection: report of three cases. Br J Dermatol 1997;136:424-7.
12. Tosti A, Piraccini BM. Proximal subungual onychomycosis due to *Aspergillus niger*: report of two cases. Br J Dermatol 1998;139:156-7.
13. Romano C, Miracco C, Difonzo EM. Skin and nail infections due to *Fusarium oxysporum* in Tuscany, Italy. Mycoses 1998;41:433-7.

14. Gianni C, Cerri A, Crosti C. Unusual clinical features of fingernail infection by *Fusarium oxysporum*. Mycoses 1997;40:455-9.
15. Nolting S, Brautigam M, Weidinger G. Terbinafine in onychomycosis with involvement by non-dermatophytic fungi. Br J Dermatol 1994;130(suppl 43):16-21.
16. De Doncker PR, Scher RK, Baran RL, Decroix J, Degreef HJ, Roseeuw DI, et al. Itraconazole therapy for pedal onychomycosis caused by some non-dermatophyte molds and in mixed infections with dermatophytes and molds: a multicenter study with 36 patients. J Am Acad Dermatol 1997;36:173-7.
17. English MP, Atkinson R. Onychomycosis in elderly chiropody patients. Br J Dermatol 1974;91:67-72.
18. Freidank H. Hyalohyphomycoses due to *Fusarium* spp: two case reports and review of the literature. Mycoses 1995;38:69-74.
19. Martino P, Gastaldi R, Raccah R, Girmenia C. Clinical pattern of *Fusarium* infections in immunocompromised patients. J Infect 1994;24(suppl 1):7-15.
20. Hennequin C, Lavarde V, Poirot JL, Rabodonirina M, Datry A, Aractingi S, et al. Invasive *Fusarium* infections: a retrospective survey of 31 cases. J Med Vet Mycol 1997;35:107-14.

AMERICAN BOARD OF DERMATOLOGY EXAMINATION DATES

In 2000, the Certifying Examination of the American Board of Dermatology (ABD) will be held at the Holiday Inn O'Hare International in Rosemont, Illinois, on Oct 29 and 30, 2000. **The deadline for receipt of applications is May 1, 2000.**

The next examination for subspecialty certification in Dermatopathology will be held in Tampa, Florida, on Friday, Nov 10, 2000. **The deadline for receipt of applications is July 1, 2000.**

The date of the next examination for subspecialty certification in Clinical and Laboratory Dermatological Immunology has not been determined.

The next Recertification Examination of the ABD will be held in 2001. **The deadline for receipt of applications is March 1, 2001.**

For further information about these examinations, please contact:
Harry J. Hurley, MD
Executive Director
American Board of Dermatology
Henry Ford Hospital
1 Ford Place
Detroit, MI 48202-3450
Telephone: 313-874-1088
Fax: 313-872-3221