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TREATMENT AND SEROLOGICAL STUDIES OF AN ITALIAN CASE OF PENICILLIOSIS MARNEFFEI CONTRACTED IN THAILAND BY A DRUG ADDICT INFECTED WITH THE HUMAN IMMUNODEFICIENCY VIRUS

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A case of disseminated penicilliosis marneffei, the first to be diagnosed in Italy, is described in a male HIV-positive drug addict. The patient had visited Thailand several times in the two years prior to his hospitalization. The presenting signs were fever, productive cough, facial skin papules and pustules, nodules on both thumbs and oropharyngeal candidiasis.

Penicillium marneffei was isolated from a series of blood specimens with the lysis centrifugation procedure. Septate, yeast-like cells were observed in histological sections of the nodules and sputum smears.

The patient was treated for 6 weeks with amphotericin B (total dosage 1,400 mg) and flucytosine (150 mg/kg/die) for the first 3 weeks. Prompt clinical improvement and sterilization of all biological specimens were attained. Itraconazole was administered as maintenance therapy (400 mg/die for the first month and 200 mg afterward). During the follow-up period, no relapse was observed. The patient, however, did succumb to a variety of non-mycotic infections and died nine months after start of therapy. At autopsy, *P. marneffei* was not detected in his tissues.

Serological studies were performed with a micro-immunodiffusion procedure using a mycelial culture filtrate antigen of *P. marneffei*. Sera taken early in the course of the disease gave positive antibody reactions. Whereas sera taken 3-5 months following therapy were negative.

All known cases of penicilliosis marneffei in bamboo rats and in humans among the inhabitants and visitors to the endemic areas of *P. marneffei* in South East Asia and Indonesia are summarized.

INTRODUCTION

Penicilliosis marneffei is a mycotic disease caused by *Penicillium marneffei*, the sole dimorphic species among the penicillia (3, 29, 30). It was first discovered in 1956 as a disease agent of captive, wild-caught bamboo rats (*Rhizomys sinensis*) in Vietnam (3). Subsequent studies of wild rodent infections and human cases of penicilliosis marneffei have revealed that its etiologic agent is also endemic in Southeastern

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TABLE 1. - Currently known areas endemic for *Penicillium marneffei.*

Endemic Countries	Human and Bamboo Rat Hosts	Ref.*
China	Humans and *Rhizomys pruinosus*	11, 20
Hong Kong	Humans	7, 45
Indonesia	Human (transient visitor)	2
Thailand	Humans, *Cannomys badius, R. pruinosus*	1, 18
Vietnam	*Rhizomys sinensis*	29, 30

*Selected references.

China's Guangxi Zhuang Autonomous Region, Hong Kong, Indonesia, and Thailand (Table 1).

In 1973, the first known spontaneous human case was diagnosed in Columbia, South Carolina, USA, in a minister suffering from Hodgkin's disease (13). This individual had toured unspecified Asian countries during the summer of 1970. Subsequent to this case, 34 autochthonous and heterochthonous cases of penicilliosis marneffei have been described among non-HIV+ residents or visitors to the endemic regions of Asia (Table 2). Significantly, 39 additional cases of this disease have been diagnosed in HIV+individuals; 28 cases among inhabitants of the endemic areas (Table 3) and 11 among travelers to those countries (Table 4).

We describe, in detail, a case of disseminated penicilliosis marneffei that, chronologically, was the fourth such case associated with the acquired immunodeficiency syndrome (AIDS) (9, 42).

TABLE 2. - Compilation of autochthonous (A) and heterochthonous (H) cases of penicilliosis marneffei unassociated with AIDS.

Year	Homeland	Region Where Infected	No. Cases*	Ref.**
1973	United States (H)	South East Asia	1	13, 14
1984	United States (H)	Far East	1	24
1984	Thailand (A)	Thailand	5	18, 37
1985	Hong Kong (A)	Hong Kong	1	34
1985	China (A)	China	8	10
1985	China (A)	China	1	44
1986	Hong Kong (A)	Hong Kong	1	45
1988	China (A)	China	4	12
1988	Hong Kong (A)	Hong Kong	1	39
1989	Hong Kong (A)	Hong Kong	1	4, 5
1989	Taiwan (?)	China, Hong Kong or Taiwan?	1	21, 43
1990	Hong Kong	Hong Kong	2	6, 7
1991	Canada (H)	Thailand	1	33
1991	Canada (H)	China	1	23
1992	Thailand	Thailand	5	36

* Total number of cases - 34

** Original reference and additional reference, where cited, concerning the same case or some of them.

TABLE 3. - Cases of autochthonous penicilliosis marneffei in HIV+ inhabitants.

Year	Endemic Country	No. Cases*	Ref.**
1989	Thailand	1	28
1991	Thailand	5	8, 36
1991	Hong Kong, Vietnam (India, South Africa, South America)***	2	40
1991	Hong Kong	1	22, 41
1992	Thailand	16	36
1992	Hong Kong	3	41

* Total number of cases - 28;
** Original reference and additional reference, where cited, concerning the same case or some of them;
**** Countries also visited but not known to be endemic.

TABLE 4. - Cases of heterochthonous penicilliosis marneffei in HIV+ visitors to the Asian endemic areas.

Year	Homeland	Region Where Infected	No. Cases*	Ref.**
1988	United Kingdom	China or Hong Kong	1	25
1988	France	Indonesia	1	2
1988	United States	?***	1	26
1989	Italy	Thailand	1 (present case)	9, 42
1989	France	Thailand (India, Myanmar)***	1	27, 35
1990	Netherlands	Thailand	1	17
1991	France	Thailand	1	38
1991	France	South East Asia	2	16
1992	Netherlands	Indonesia (Sumatra)	2	19

* Total number of cases - 11;
** Original reference and additional reference, where cited, concerning the same case or some of them;
*** No anamnestic travel data provided;
*** Countries also visited but not known to be endemic.

Case report

A 33 year old male, an intravenous drug abuser, HIV positive, was admitted to the 1st Department of Infectious Diseases of the Ospedale L. Sacco of Milan, Italy, in July, 1988 with a *Pneumocystis carinii* pneumonia. The patient was successfully treated with a 3 week course of trimethoprimsulfamethoxazole, and then discharged. Two months later he was readmitted with a history of ten days of prolonged fever (37.5 - 38° C), a productive cough, and a facial maculopapular, pustular rash, that was predominantly in a crusty phase. In addition to the cutaneous eruption, physical examination revealed mild hepatomegaly, generalized adenopathy, two nodular lesions on both thumbs, and oropharyngeal candidiasis.

Laboratory investigations showed a marked increase of the erythrosedimentation rate (94 mm at the 1st h), moderate anemia (Hb 9.7 g/dl) with normochromic and normocytic red blood cells, leukopenia (2100 cells/mm3) with lymphopenia (11.8%) and thrombocytopenia (82.000/mm^3). The T-cell subset revealed a marked depression of CD4+(12/µl, 5.04%) and CD8+ (46/µl, 18.66%) and a CD4+/CD8+ ratio of 0.32. A skin test performed with Multitest Merieux, showed total anergy.

During the first week of hospitalization, the patient's fever remained at a low level (37.5 - 38° C) and the microbiological investigations gave negative results. Subsequently, the fever rapidly increased to 39° C and the patient developed clinical signs of pneumonia. A chest x-ray revealed consolidation of the inferior dorsal lobe of the left lung.

Blood cultures, obtained by the lysis centrifugation system (Isolator System, Dupont), gave rise to numerous colonies of a *Penicillium* sp. that on Sabouraud dextrose agar (SDA) with 4 mg/100 ml of chloramphenicol (Becton Dickinson) produced a diffusible, red pigment. The fungus was repeatedly isolated from 6 other blood cultures performed with the same method over the following days. In addition, the same mould was isolated from sputa, scrapings from the facial skin lesions, and biopsied tissue from one of the thumb nodules. Yeast-like cells were observed in the histological sections of the nodule stained with the Gomori methenamine silver stain (GMS) procedure (Figures 1, 2). The diagnostically important septate yeast-like cells, that characterize the tissue form cells of *P. marneffei*, were scattered in small numbers among the more numerous non-dividing yeast-like cells present. These cells measured 2.5 to 5 µm in diameter. The septations of the dividing cells distinguish them from the similar sized tissue form cells of the *capsulatum* variety of *Histoplasma capsulatum* which multiply by a budding process.

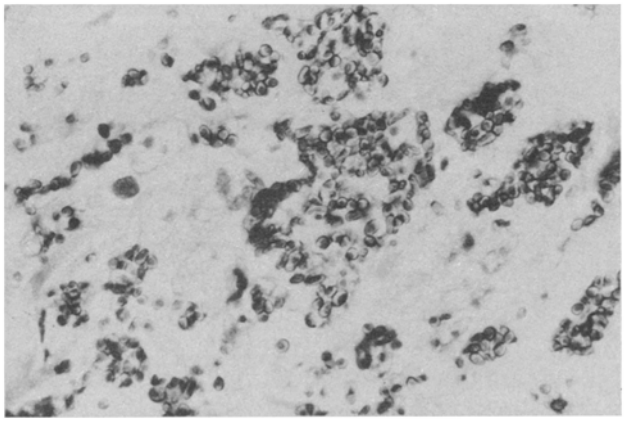

Figure 1. - Clusters of tissue form cells of *Penicillium marneffei* in a histological section of the nodule from a finger of the patient with disseminated penicilliosis marneffei. Original magnification x 940, GMS.

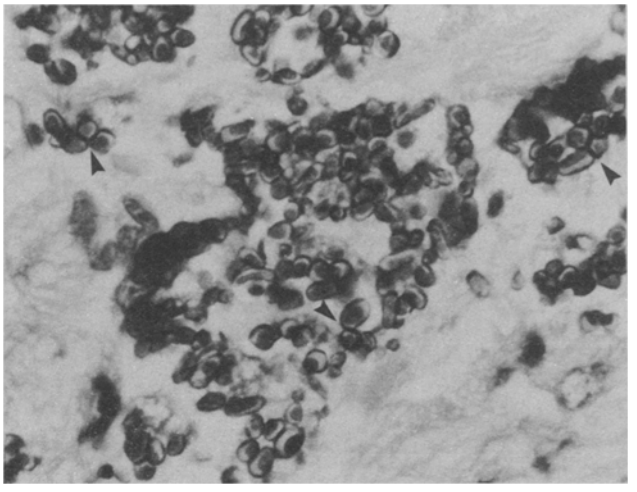

Figure 2. - Higher magnification of the central cluster of *Penicillium marneffei* tissue form cells depicted in Figure 1. Note the septation (arrows) in the cells dividing by schizogony rather than a budding process. Original magnification x 2000, GMS.

Mycologic studies

The isolate (IUM - 885346), recovered from blood, was subcultured on SDA. The colonies at 25° C were initially moist, becoming finely powdery, grayish pink and measured 37-39 mm in diameter after 2 weeks. Their reverse was pink to red with a prominent soluble red pigment diffusing into the medium. Slide cultures on Czapek's Dox agar after 2 weeks at 25° C showed hyaline, septate hyphae bearing lateral and terminal conidiophores. The conidiophores consisted of basal stipes bearing terminal verticils of 3-5 metulae. Some subterminal metulae bore 5-7 phialides in a verticillate manner. Basipetal chains of smooth, spherical to ellipsoidal conidia were produced from the tips of the phialides. The conidia measured 2-4 x 2-3 µm.

On Brain heart infusion agar at 37° C, the colonies were yeast-like, white to tan becoming cerebriform. Microscopically, growth was yeast-like, consisting of tubular, oval to oblong cells dividing by a fission rather that a budding process. Based on its dimorphic nature, production of a red diffusible pigment and the morphology of the filamentous and yeast-like forms, the isolate (IUM - 885346) was identified as *P. marneffei.*

The identification, centered on morphological and physiological findings, was further confirmed by use of Sekhon et al's exoantigen test (32). The exoantigen extract from a slant culture of IUM - 885346 was tested by the reverse microimmunodiffusion procedure against rabbit anti-*P marneffei* reference serum in the presence of appropriate reference antigens. The patient's isolate produced two precipitin lines of identity with the *P. marneffei* reference system. Culture IUM - 885346 is deposited in the Mycotic Diseases Branch's culture collection under accession number CDC B - 4727 and in the Institute of Hygiene and Epidemiology, Brussels, Belgium under accession number IHEM 4176.

Therapy

The patient was treated for 6 weeks with intravenous amphotericin B (total dose 1,400 mg) combined with flucytosine (150 mg/kg/die) during the first 3 weeks. During treatment, cultural examinations of blood, sputum and urine were performed weekly. Prompt decrease of fever and clearance of clinical and

radiological signs of pneumonia were obtained. After 20 days of therapy, all biological samples became negative for *P. marneffei.* Concurrently, the cutaneous lesions were completely cured. Since itraconazole was proven *in vitro* to be highly active against the patient's isolate of *P. marneffei* with complete inhibition of the fungus at 0.01 µg/ml (test performed by Dr. J. Van Cutsem, Janssen Pharmaceutica, Beerse, Belgium), the patient was given this triazole for maintenance therapy. The daily dose was 400 mg during the first month of therapy and 200 mg afterwards.

During the follow-up, no relapse of the fungal infection was observed. The patient, however, developed several opportunistic infections, namely pulmonary tuberculosis, ophthalmic herpes zoster, and a second *Pneumocystis carinii* pneumonia, together with progressive cachexia. The patient died in April, 1989. At autopsy, interstitiopathy and multifocal suppurative pneumonia were reported, but no evidence of *P. marneffei* in tissue was found.

Serologic studies

Thirteen sera, collected over a five month period, were tested for *P. marneffei* antibody undiluted and twice concentrated with a microimmunodiffusion test (Table 5) (31, 37). In that test, a specific concentrated filtrate of *P. marneffei* antigens, and a reference rabbit antiserum containing 6 precipitins were used. Three of the 13 sera were positive undiluted and 7, including the above 3, were positive after 2X concentration. The positive sera all produced a line of identify with one of the reference precipitates. The patient was positive for *P. marneffei* antibody prior to administration of antifungal therapy and for approximately two months after its initiation. Five sera taken 3-5 months following start of therapy were antibody negative. The patient was positive for *P. marneffei* antibody early in the disease. It is interesting to note that the disappearance of antibody occurred with elimination of the infectious agent.

TABLE 5. - Microimmunodiffusion test results on sera from the AIDS patient with penicilliosis marneffei.

Dates mo/d/y	Precipitin Responses* 1:1	2X Concentration
10/14/88	+ (Weak)	+ (diffuse)
10/18/88**	+ (Weak)	+ (diffuse)
11/02/88	-	+
11/10/88	-	+
11/12/88	-	+
11/21/88	+ (Weak)	+
12/08/88	-	-
12/21/88	-	+
01/11/89	-	-
01/19/89	-	-
02/08/89	-	-
03/08/89	-	-
03/15/89	-	-

* Tests performed with antigen lot 5-84;
** Treatment initiated on this date.

DISCUSSION

Currently, *Penicillium marneffei* is known to be geographically restricted to Southeast Asia and Indonesia. Naturally acquired penicilliosis marneffei has only been reported in patients who resided in, or had visited the endemic areas. Our patient had visited Chang Mai, Thailand, a city in the Golden Triangle, 129 kilometers (80 miles) east of Myanmar (Burma), several times during the previous two years prior to hospitalization. Soon after his last visit in January, 1988, he developed a facial dermatosis, that persisted until he was hospitalized. At admission, penicilliosis marneffei was not suspected. His clinical manifestations were suggestive of an infective invasive process similar to tuberculosis or other systemic infection. Being unaware of penicilliosis marneffei, the clinicians did not consider the significance of his anamnestic travel data. The skin manifestations were also under evaluated. The first blood culture isolation attempts, performed with the Bactec NR6 and NR7 methods, remained sterile. Only when the patient's blood was processed with the lysis centrifugation blood culture method (Isolator System, Dupont) was the etiologic agent isolated. This last method proved to be highly effective as *P. marneffei* was isolated from all of the 7 blood specimens tested with this method, but from none of the 5 HemoBactec tests that were performed in parallel.

In a United States wide survey of clinical laboratory methodologies for diagnosing fungal infections, Goodwin *et al.* (15) reported that the lysis centrifugation blood culture method proved to be more advantageous than the other systems that were utilized by the participating hospitals (radiometric, biphasic and infrared) on the basis of rapid turnaround time and excellent sensitivity for *Candida* spp., *Cryptococcus neoformans* and *Histoplasma capsulatum* var. *capsulatum.* Our experience with the Milan case of penicilliosis marneffei clearly indicated that *P. marneffei* may be added with assurance to the list of pathogenic fungi that the lysis centrifugation method can effectively and rapidly recover from blood specimens.

The history of our case highlights the need to establish an early diagnosis of penicilliosis marneffei in HIV infected individuals due to their inherent susceptibilities to opportunistic infections by fungi and other organisms. A conscientious effort should be

made to determine whether a patient has lived in or visited the known Asian and Indonesian endemic areas or adjacent countries where this apparently geophilic fungus also may be reasonably expected to occur - Cambodia, India, Laos, Malaya and Myanmar.

Due to the high frequency of *P. marneffei* infections encountered in HIV positive individuals, some authors (36, 42) ventured to suggest that penicilliosis marneffei should "be added to the list of indicator diseases for the differential diagnosis of AIDS".

In patients afflicted with penicilliosis marneffei, amphotericin B alone or combined with flucytosine is considered to be the therapy of choice. Ketoconazole (27) and itraconazole (36) may be considered effective alternatives, if absorption of these drugs is assured.

Our study also indicates that HIV positive patients infected by *P. marneffei* can be positive for *P. marneffei* antibody and that serologic tests, thus, can be of diagnostic and prognostic value.

As the AIDS pandemic waxes and spreads throughout the known and suspected endemic areas of *P. marneffei*, opportunistic infections by this invasive mould will be found with heightened incidence and prevalence in the HIV positive inhabitants and visitors to those areas. Physicians and diagnostic laboratories everywhere should be prepared to consider most fungi isolated from these individuals as potential etiologic agents and in particular to suspect penicilliosis marneffei in such patients with a history of having lived or traveled in South East Asia and Indonesia.

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Added in Proofs: Three additional cases of autochthnous cases of penicilliosis marneffei in China's Guangxi Zhuang Autonomous Region unassociated with AIDS.

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