Mycopathologia **131:** 1–8, 1995.

Occurrence of *Penicillium marneffei* infections among wild bamboo rats in Thailand

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Received and accepted 18 May 1995

Abstract

Penicilliosis marneffei has emerged as an endemic systemic mycosis in Southeast Asia among humans and wild bamboo rats. To gain an insight into the epidemiology of this life-threatening disease, a survey of bamboo rats for natural infections by *Penicillium marneffei* was carried out in the central plains of Thailand during June–September, 1987. Thirty-one lesser bamboo rats (*Cannomys badius*) and eight hoary bamboo rats (*Rhizomys pruinosus*) were trapped. Portions of their internal organs were cultured to determine if they had been infected by *P. marneffei*. Six each of *C. badius* (19.4%) and *R. pruinosus* (75%) yielded cultures of this unique, dimorphic *Penicillium* species. All of the isolates were readily converted to their unicellular form that multiplies by the process of schizogony by incubating them at 37 °C on plates of brain heart infusion agar. Their identity was further confirmed by a specific immunological test. Among the internal organs of the positive rats, the lungs had the highest positivity (83.3%), next in decreased order of frequency were the liver (33.3%) and the pancreas (33.3%). The use and value of domestic and wild animals in locating and demarcating endemic areas of geophilic fungal pathogens are discussed. Penicilliosis marneffei is considered to be a zooanthroponosis – a disease that occurs in lower animals, as well as, humans.

Key words: Bamboo rats, Natural animal infections, *Penicillium marneffei*, Thailand

Introduction

The first isolate of *Penicillium marneffei* was recovered in 1956 from a captive Chinese bamboo rat (*Rhizomys sinensis*) in Vietnam [1]. The native, wild-caught rodent had been experimentally inoculated with the scrub typhus bacterium – *Rickettsia orientalis*, now designated as a synonym of *R. tsutsugamushi*. The rat died 23 days later. At autopsy, it was found to have an enlarged liver, and spleen, viscous ascitic fluid and epiploic nodules. All of the rat's organs and ascitic fluid yielded a *Penicillium* species, that proved to be pathogenic to hamsters (*Mesocricetus auratus*). Previous to this occurrence, two other captive uninoculated Chinese bamboo rats had died showing signs of illness. At their autopsy, a slightly hypertrophic spleen, ascites and epiploic nodules showed unicellular, fungal cells in their macrophages. These tissues, however, were not cultured. The *Penicillium* isolate was sent to the Institut Pasteur in France, where it was studied and described as a new species [2, 3]. It was named *P. marneffei* in honor of Dr. Hubert Marneffe, the director of the Institut Pasteur of French Indochina. Further *in-vitro* and *in-vivo* studies revealed *P. marneffei* to be a dimorphic mould with a unicellular form not unlike that of the *capsulatum* and *farciminosum* varieties of *Histoplasma capsulatum* [4]. Of utmost taxonomic and diagnostic significance, its yeast cells, however, divided by schizogony and not by budding.

Thirty years later in 1986, Deng *et al.* [5] investigated bamboo rats in China's autonomous region of Guanxi Zhuang to determine their interrelationship, if any, to *P. marneffei*. The only rats captured were identified as the hoary bamboo rat – *R. pruinosus*. Of the 19

trapped rats, 18 yielded cultures (94.7%) of *P. marneffei* from one or more of their internal organs; liver, lung, mesenteric lymph nodes, pancreas and spleen. In life, these rats had appeared healthy and asymptomatic. It was concluded that both humans and bamboo rats are, in all probability, infected from a common source in nature. In 1988, Deng *et al.* [6] reported, without any elaboration, the isolation of *P. marneffei* "from soil from three burrows of bamboo rats" (*R. pruinosus* – personal communication from Z.L. Deng). These investigators also stated that their "results suggest a common environmental source of infection for bamboo rats and people".

Following the discovery of human infections by *P. marneffei* in Thailand in 1984 [7], a survey of bamboo rats for natural infections by this fungus was carried out in central Thailand during the period of June–September 1987. In this report, we describe the results of that investigation.

Materials and methods

Professional trappers were contracted to capture bamboo rats in the Central Plains' provinces of Kanchanaburi, Lopburi and Prachuap Khri Khan (Fig. 1).

Once received in the laboratories of Mahidol University, Department of Clinical Microbiology in Bangkok, the rats were killed with ether and autopsied. Their adrenal glands, heart, kidneys, liver, lungs, pancreas and spleen were removed and 4 small pieces of each organ were cultured on plates of Sabouraud dextrose agar (SDA) and incubated at 25 °C. The plates were examined periodically and all fungal colonies, suspected of being *P. marneffei*, were subcultured and incubated on plates of SDA at 25 °C and brain heart infusion agar (BHI) at 37 °C. On the basis of the gross and microscopic features of the 25 °C colonies and their counterparts at 37 °C on BHI agar, the isolates were tentatively identified as *P. marneffei*. Subcultures were then airmailed for further study to the Centers for Disease Control and Prevention's, Mycology Reference Laboratory in Atlanta, Georgia.

Results

In Atlanta, all of the isolates were subcultured on SDA at 25 °C. The colonies at first were moist but their surface soon became finely powdery, often umbonate and radially striated, and grayish pink. Their reverse was pink to red; the result of the production of a red soluble pigment that diffused into the medium. Microscopically, the conidiophores were borne on the surface of vegetative hyphae laterally and terminally. Their stipes were up to 180 μm long, smooth, bearing terminal verticils of 3 to 5 metulae. The metulae measured 7–15 × 2.5–3.5 μm, often up to 25 μm long; bearing phialides in verticils. The phialides were ampulliform, smooth-walled, measured 6–8 × 3–3.5 μm and bore short disarrayed chains of conidia. The conidia were ellipsoidal, smooth, and measured 2.5–4 × 2–3 μm.

When the isolates were grown on BHI agar at 37 °C, their colonies became yeast-like and white to tan with a smooth to cerebriform surface. Microscopically, growth was found to be in the form of tubular to oblong, yeast-like cells that divided by fission rather than a budding process. Based upon the morphologic features of their mycelial form, production of a red diffusible pigment and the dimorphic nature of the isolates, they were confirmed as *P. marneffei*. Exoantigens, prepared from all of the isolates, were tested against reference rabbit anti-*P. marneffei* antisera and reference antigens with a micro-immunodiffusion procedure [8, 9]. All of the antigenic extracts produced two to four precipitin lines of identity with the reference system.

Thirty-nine bamboo rats were captured in the provinces of Kanchanaburi, Lopburi and Prachuap Khri Khan (Fig. 1). Thirty-one of these rodents were identified as *Cannomys badius* – the lesser bamboo rat and 8 proved to be hoary bamboo rats – *Rhizomys pruinosus*. All of the *C. badius* rats were captured in the province of Lopburi. While the eight *R. pruinosus* rats originated in the provinces of Kanchanaburi – 4, Lop Buri – 1 and Prachuap Khri Khan – 3.

Six of the 31 *C. badius* rats (19.4%) and 6 of the 8 *R. pruinosus* rats (75%) yielded verified isolates of *P. marneffei*. The cultural results by organs are presented in Table 1. In descending order of frequency, only three of the organs proved positive for *P. marneffei*. These were the lungs (83.39%), liver (33.3%) and the pancreas (33.3%). The spleens surprisingly gave negative results.

Discussion

Recovery of *P. marneffei* from the internal organs of wild caught lesser bamboo rats (*C. badius*) has added a new rat genus and species to the list of rodents that are currently known to be susceptible to infection by this

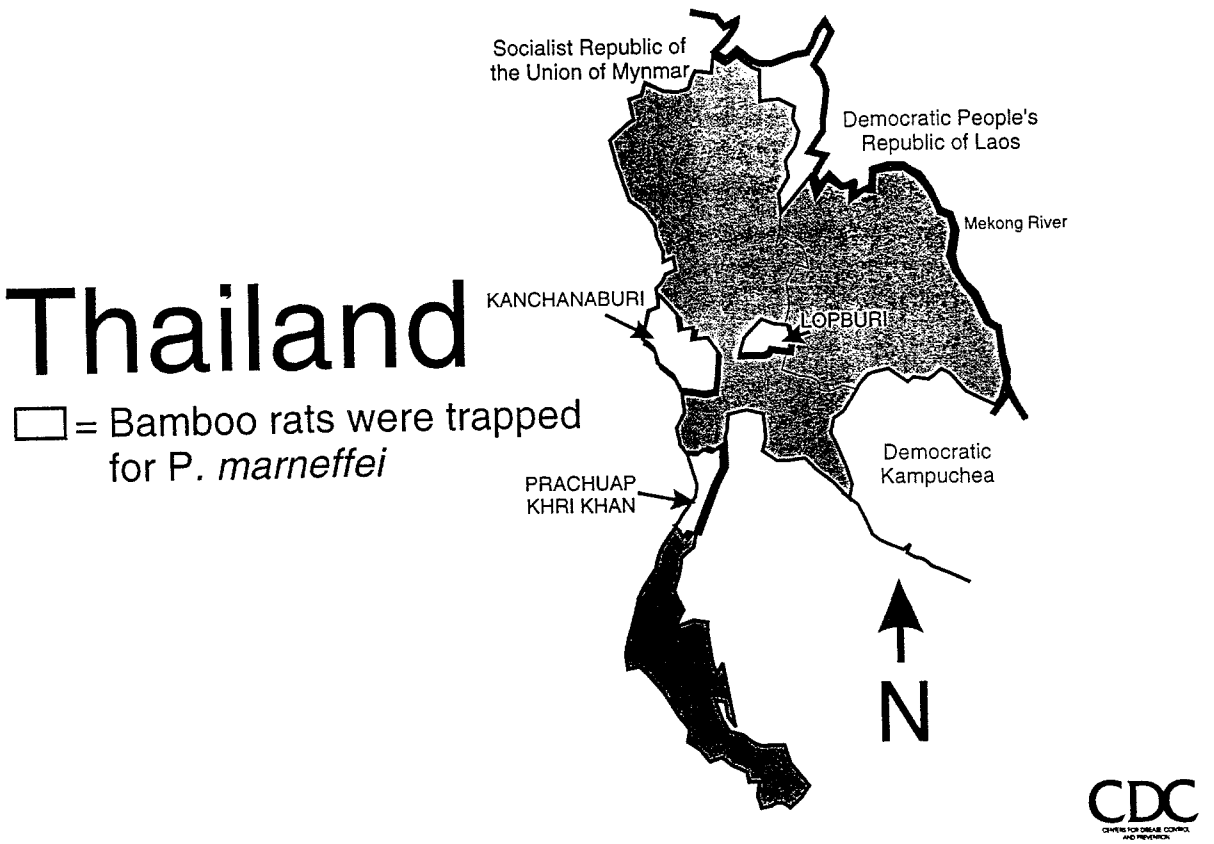

Fig. 1. Location of the Thai provinces of Kanchanaburi, Lopburi and Prachuap Khri Khan where *Cannomys badius* (Lopburi –31), the lesser bamboo rat and *Rhizomys pruinosus* (Kanchanaburi–4, Lopburi –1, Prachuap Khri Khan –3) the hoary bamboo rat, were captured.

Table 1. Organs (%) of *Cannomys badius* (C) and *Rhizomys pruinosus* (R) found to be culture positive for *Penicillium marneffei*

Positive rats	Adrenals	Heart	Kidneys	Liver	Lungs	Pancreas	Spleen
C-12	–	–	–	–	+	–	–
C-15	–	–	–	–	+	–	–
C-17	–	–	–	+	+	+	–
C-25	–	–	–	–	+	+	–
C-37	–	–	–	+	–	+	–
C-41	–	–	–	–	+	–	–
R-1	–	–	–	+	–	–	–
R-2	–	–	–	+	+	–	–
R-3	–	–	–	–	+	–	–
R-6	–	–	–	–	+	–	–
R-23	–	–	–	–	+	–	–
R-29	–	–	–	–	+	+	–
No. cultured/ No. +, %	12/0, 0%	12/0, 0%	12/0, 0%	12/4, 33.3%	12/10, 83.3%	12/4, 33.3%	12/0, 0%

Table 2. Chronological reports of bamboo rats found to be infected by *Penicillium marneffei*

Year	Genus and species	Country	No. + rats/No. = % +	Ref.
1956	*Rhizomys sinensis*	Vietnam	1/1 = 100%	1
1986	*R. pruinosus*	China	18/19 = 4.7%	5
1987	*Cannomys badius*[a]	Thailand	6/31 = 19.4%	10
1987	*R. pruinosus*[a]	Thailand	6/8 = 75.0%	10
1987	*R. pruinosus*	China	114 / 179 = 63.7%	11
1988	*R. sinensis*	China	2/2 = 100%	6[b]
1990	*R. pruinosus*	China	15/16 = 93.8%	12

[a]Present study.
[b]Personal communication from Z.L. Deng.

Table 3. Lower animal hosts of dimorphic systemic pathogenic fungi

Dimorphic fungi	Hosts	Ref.[a]	Dimorphic fungi	Hosts	Ref.[a]
Blastomyces	**Domestic animals**			wild animals	
dermatitidis	Cats (*Felis domesticus*)	14		Coyotes (*Canis latrans*)	28
	Dogs (*Canis familiaris*)	15–17		Otter, California sea (*Enhydra lutris*)	29
	Horses (*Equus caballus*)	18		Peccary (*Tayassu tajacu*)	30
	Wild animals			Rodents	
	Bat (*Rhinopoma hardwickei*)	19		*Dipodomys merriami* (kangaroo rat)	31
	Deer (*Odocoleus virginianus*)	20		*Onchomys torridus* (grasshopper mouse)	32
	Wolf (*Canis lupus*)	21		*Perognathus baileyi* (pocket mouse)	31
Coccidioides immitis	**Domestic animals**			*P. intermedius* (pocket mouse)	31
	Cats	22		*P. penicillatus* (pocket mouse)	31
	Cattle (*Bos taurus*)	23		Snake	
	Dogs	24		Sonoran gopher snake (*Pituophis*	33
	Horses	25		*melanoleucus affinis*)	
	Sheep (*Ovis aries*)	26	*Histoplasma capsulatum*	Domestic animals	
	Swine (*Sus scrofa*)	27	var. *capsulatum*	Cat	34
	Cow	35		**Bats**	
	Dog	34		*Carollia perspicillata*	44
	Horse	34		*Chilonectria rubiginosa*	44
	Rabbit (*Oryctolagus cuniculus*)	36		*Desmodus rotundus*	44
	Swine	37		*Eptesicus fuscus*	45
	Wild animals			*Glossophaga soricina*	44
	Armadillo, seven banded	38		*Leptonycteris sanborni*	46
	(*Dasypus hybridus*)			*Lonchophylla robusta*	47
	Armadillo, nine banded	39		*Lonchorhina aurita*	44
	(*D. novemcinctus*)			*Macrotus waterhousei*	48
	Badger (*Meles meles*)	40		*Micronycteris megalotis*	49
	Bats			*Molossus ater*	50
	Artibeus jamaicensis	41		*M. daulensis*	51
	Brachyphylla cavernarum	42		*M. major*	52
	B. nana	43		*Mormoops blainvillii*	43
				Myotis austroriparius	45

[a]Selected references.

Table 3. Continued

Dimorphic fungi	Hosts	Ref.[a]	Dimorphic fungi	Hosts	Ref.[a]
	M. grisescens	45	*Histoplasma capsulatum*	**Wild animals**	
	M. lucifugus	45	var. *capsulatum*	Fox, grey (*Urycon cinereoargentus*)	56
	Myotis myotis	53		Fox, red (*Vulpes fulva*)	57
	M. sodalis	45		Hedge hog, (*Erinaceus europaeus*)	58
	Noctilio labialis	47		Mice, field (*Mus musculus*)	56
	Nycticeius humeralis	45		Mice, white footed (*Peromyscus*	59
	Phyllostomus discolor	41		*leucopus*)	
	P. hastatus	49		Monkey, long tailed (*Cercopithecus*)	60
	Pipistrellus subflavus	54		*neglectus*)	
	Pteronotus rubiginosa	47		Opossum, wooly (*Caluromys*	61
	P. suapurensis	47		*derbianus*)	61
	Saccopteryx bilineata	50		Opposum, common (*Didelphis*	61
	Tadarida brasiliensis	55		*marsupialis*)	
	T. yucatanica	47		Opposum, Virginia	59
	Tonatia bidens	47		(*Didelphis virginiana*)	
	Opposum, four eyed	61		Sloth, two-toed (*Choloepus didactylus*)	62
	(*Philander opposum*)			Squirrel, thirteen lined ground	59
	Paca (*Agouti paca*)	62		(*Citellus tridecemlineatus*)	
	Raccoon (*Procyon lotor*)	59		Woodchuck (*Marmota monax*)	56
	Rat, brown (*Rattus norvegicus*)	63	*Histoplasma*	**Domestic animals** – None	
	Rat, roof (*R. rattus*)	64	*capsulatum* var. *duboisii*	**Wild animals**	
	Rat, spiny	62		Baboon, yellow (*Papio cynocephalus*)	65, 66
	(*Prochimys guyannensis*)			Baboon, western (*P. papio*)	67
	Rat, spiny (*P. semispinosus*)	61		Bat (*Nycteris Hispida*)	68
	Shrew, short tailed	59	*Paracoccidioids*	**Domestic animals** – None	
	(*Blarina brevicauda*)		*brasiliensis*	**Wild animals**	
	Skunk, spotted	64		Armadillo, nine banded (*Dasypus*	69
	(*Spilogale putorius*)			*novemcinctus*)	
	Skunk, stiped	56			
	(*Mephitis mephitis*)				

[a]Selected references.

apparently geophilic mould (Table 2). Thus, according to the epidemiologic classification of diseases developed by Pavlovsky [13], penicilliosis marneffei is a zooanthroponosis; a term that he applied to diseases that are both common to lower animals and humans. Among the systemic mycoses caused by dimorphic fungi that are also classifiable as zooanthroponoses, one can cite blastomycosis, coccidioidomycosis, histoplasmosis capsulati, histoplasmosis duboisii, and paracoccidioidomycosis. Their domestic and wild animal hosts are quite a varied lot as noted to Table 3.

It is quite evident that many domestic and wild animals are as susceptible to pathogenic fungi as humans. Those that burrow into soil are especially vulnerable since the major systemic pathogenic moulds are geophilic. That is to say, they live, multiply and survive in soil as saprophytes. Advantage can be taken of the geophilism of such fungi to seek and map out their geographic distribution and to discover their ecologic niches with the aid of such animals as rodents. Use of wild animals as sentinels and detectors of pathogenic fungi is especially useful when skin test antigens have not been developed or are not available for use in ecologic and epidemiologic surveys. This is especially true in the case of penicilliosis marneffei. As yet, there is no equivalent to coccidioidin and histoplasmin to map out the prevalence and geographic distribution of infections caused by *P. marneffei*. Animal culture surveys, however, can be substituted for human skin test surveys with comparative ease and with assured

specificity. Such surveys, as cited in Table 3, have proven invaluable for discovering and gaining insights into the prevalence of pathogenic fungi in given areas and eventally discovering their ecologic niches [31, 70, 71], especially when they are correlated with selectively isolate systemic fungal pathogens from soil [72].

The isolation of *P. marneffei* from three species of bamboo rats in China, Thailand and Vietnam substantiates the value of animals as epidemiological markers. In this conjunction it is pertinent to note the geographic distribution of the species of bamboo rats. These Asian endemics are classified in the genera *Cannomys* and *Rhizomys* [73]. The genus *Cannomys* is monotopic and *C. badius* – its lone species – is described as occurring in northern Bangladesh, India (state of Assam), Laos, Myanmar (Burma), Nepal, Thailand and northern Vietnam. The three species of *Rhizomys* are geographically distributed as follows: *R. pruinosus* from northeast India (the state of Assam) to southeastern China and down through the Malay Peninsula, which comprises Cambodia, Laos, Malaysia, Myanmar, Thailand and Vietnam; *R. sinensis* – occurs in central and southern China, northern Myanmar and Vietnam; *R. sumatrensis* (Sumatran bamboo rat) is found in Cambodia, Indonesia (island of Sumatra), Laos, Malaysia, Myanmar, Thailand and Vietnam.

Surveys of these rats in Assam, Bangladesh, Cambodia, Laos, Malaysia, Myarmar, Sumatra, Thailand and Vietnam would be of public health importance and, if productive of *P. marneffei*, would alert physicians and medical microbiologists to the possible occurrence of concurrent human cases of penicilliosis marneffei. There is no plausible reason to assume that *P. marneffei* is restricted geographically only to its currently known endemic areas – China, Hong Kong, Indonesia, Thailand and Vietnam [10]. As public health workers become aware of the existence of penicilliosis marneffei and of its pathognomonic characteristics [10, 74], new areas of endemicity will be uncovered.

Animal studies are especially useful in areas with low levels of infestation by pathogenic fungi as the result of the fungi being restricted to sheltered and scattered sites. Such utility has been strikingly illustrated in Denmark [40] and Switzerland [75] by the isolation or detection of the *capsulatum* variety of *H. capsulatum* in badgers (*Meles meles*). In those two countries autochthonous human cases of histoplasmosis capsulati have yet to be reported.

Wild animal surveys, however, ought not to be restricted exclusively to bamboo rats, but other groups of animals should also be examined for infections by *P. marneffei*. They too could prove to be useful markers for the occurrence of this emerging and, as yet, incompletely defined mycotic pathogen.

Acknowledgement

Animal capture in Thailand was funded by Centers for Disease Control and Prevention Contract Order 37984.

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