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## CASE REPORT

### MULTIPLE BRAIN ABSCESSSES DUE TO *Penicillium* spp INFECTION

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#### SUMMARY

We present a case of central nervous system (CNS) infection by a member of the *Penicillium* genera in a HIV-negative man in Brazil. The patient was admitted complaining of loss of visual fields and speech disturbances. CT scan revealed multiple brain abscesses. Stereothacic biopsies revealed fungal infection and amphotericin B treatment begun with initial improvement. The patient died few days later as a consequence of massive gastrointestinal bleeding due to ruptured esophageal varices. The necropsy and final microbiologic analyses disclosed infection by *Penicillium* sp. There are thousands of fungal species of the *Penicillium* genera. Systemic penicilliosis is caused by the *P. marneffe* and was formerly a rare disease, but now is one of the most common opportunistic infection of AIDS patients in Southeast Asia. The clinical presentation usually involves the respiratory system and the skin, besides general symptoms like fever and weight loss. *Penicillium* spp infection caused by species other than *P. marneffe* normally cause only superficial or allergic disease but rare cases of invasive disease do occur. We report the fourth case of *Penicillium* spp CNS infection.

**KEYWORDS:** Penicilliosis; *Penicillium* spp; CNS infection; Fungal infection.

#### INTRODUCTION

In recent years, invasive fungal infections have become increasingly common. Concomitantly, there has been a gradual rise in the number of rare fungal infections in immunocompromised and normal patients. *Penicillium* genera aggregates thousands of fungal species, being the *P. marneffe* infection the far most important one, mainly associated with AIDS in the Southern Asia<sup>2,3,5,22</sup>. However a number of infections caused by species other than *P. marneffe* have been reported<sup>13</sup>.

In this study, we report a non-HIV patient from Brazil who had central nervous system involvement by *Penicillium* spp documented by biopsy. To our knowledge, this is the first report of central nervous system involvement by *Penicillium* spp and also the first report of invasive penicilliosis in Brazil.

#### CASE REPORT

A 41 year-old man, with chronic liver disease caused by long term HBV infection (Child-Pugh C), has presented to the Emergency Department complaining of bilateral loss of visual fields and dysphasia for three days.

On physical examination he was conscious (Glasgow Coma Scale

15), pale, dehydrated, with axilar temperature of 37 °C, heart rate of 88 bpm, blood pressure of 126 x 80 mmHg. The abdomen was tense, with signs of high volume ascites without focal tenderness. The neurological exam revealed complete right hemiparesia and expression aphasia. Pupils and retinal examination were normal.

Biochemical blood exams revealed a moderate degree of anemia and coagulopathy without any other important alterations. The liquor exam was normal and an HIV-serology was negative. A brain CT scan and MRI showed multiple lesions compatible with abscesses mainly in the subcortical regions of the brain (Fig. 1 and 2).

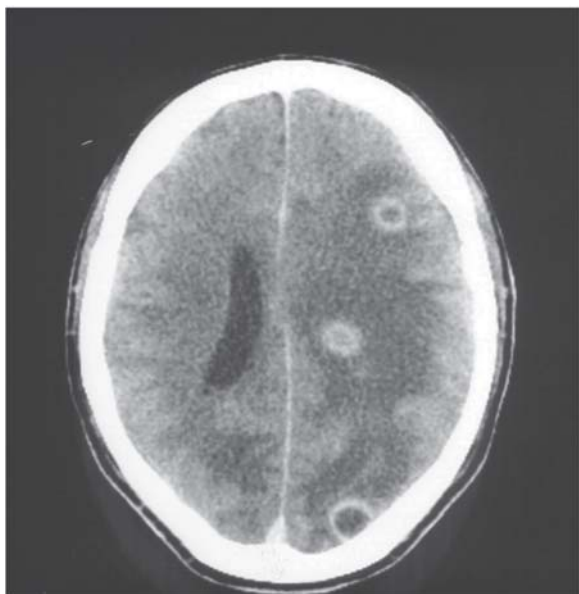
The patient was admitted to the hospital and empirical antibiotic treatment was initiated with ceftriaxone, metronidazole and vancomycin in adequate doses for central nervous system (CNS) infection. On the 2<sup>nd</sup> day the neurological signs were worse, evolving to complete right hemiplegia. A brain stereothactic biopsy was then indicated and revealed fungal infection, suggestive of *Aspergillus* or *Mucor* species. The specimen was sent to microbiological analyses. Amphotericin B was initiated with gradual initial improvement.

However, on the 15<sup>th</sup> hospital day the patient presented an important episode of hematemesis and deterioration of the consciousness level, requiring endotracheal intubation and transfer to the Surgical ICU.

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**Fig. 1** - A brain CT scan showed multiple hypodense, ring-enhancing lesions compatible with abscesses mainly in the subcortical regions.

Endoscopy revealed abundant bleeding from esophageal varices. An endoscopic elastic band ligation was unsuccessful and the patient died from refractory hemorrhagic shock few hours later.

Necropsy disclosed a diffuse brain edema and multiple brain abscesses containing septated hyphae (Fig. 3 and 4).

Growth was observed after incubating biopsy material at 30 °C on Sabouraud and Sabhi agar. Thereafter, it could be seen positivity on tube and plate with potato agar and the micromorphologic differentiation through microculture revealed *Penicillium* spp. No other microbiologic technique resulted positive.



**Fig. 2** - The T1-weighted MRI scan of the brain revealed multiple lesions suggestive of abscesses.



**Fig. 3** - At autopsy, brain abscesses with central liquefactive necrosis (arrows).

## DISCUSSION

Approximately 225 species of *Penicillium* have already been described<sup>13</sup>. Substantial numbers of *Penicillium* spores are present in the normal fungal flora of the air. Penicillia are ascomycetes closely related to *Aspergillus* but without the same invasive capabilities, with the notable exception of *P. marneffei*. We will present a brief discussion

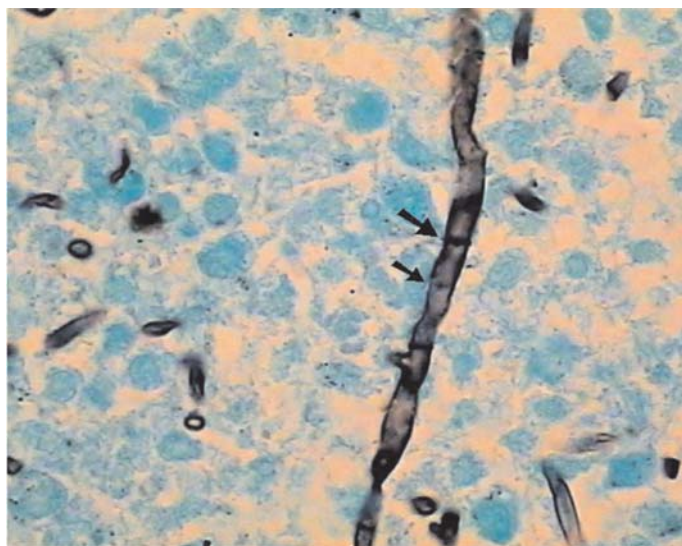


Fig. 4 - *Penicillium* colonies showing septate hyphae (arrow) were identified.

on this two clinical entities: systemic penicilliosis due to *P. marneffei* and infection due to other species of *Penicillium* (*Penicillium* spp).

**Systemic penicilliosis caused by *P. marneffei*:** Systemic penicilliosis is a fungal infection caused by the dimorphic fungi *Penicillium marneffei*, a pathogenic species of the *Penicillium* genera<sup>17</sup>. SEGRETAIN initially isolated this specie in captive bamboo rats (*Rhysomys sinensis*) at the Pasteur Institute in 1956<sup>1,18</sup>. The same author, through accidental inoculation of laboratorial fungi specimens also made the first description of human pathogenicity. Since then, few cases have been described until the emergence of AIDS epidemic widespread in that region.

In 1988, a great number of cases of systemic penicilliosis were diagnosed in patients who had lived or traveled to Southeast Asia. Between 1991 and 1997, the University Hospital of Chiang Mai reported the occurrence of 1173 cases of systemic penicilliosis, most of them related to AIDS<sup>20</sup>. Nowadays, systemic penicilliosis remains one of the most common opportunistic infections on late HIV-infected patients in endemic areas, such as China, Hong Kong, Taiwan and Malasia<sup>10,11,15,20,25</sup>.

*Penicillium marneffei*, like other endemic fungal species, lives in the soil. According to the actual evidences, it directly infects both of host species, bamboo rats and humans. Therefore, there seems to be no role for the rats on the natural occurring human disease. Like other pathogenic fungi, the conidia are inhaled and internalized by alveolar macrophages and transported to the reticuloendothelial system. The microorganism can then proliferate as soon as a host immune deficiency takes place, leading to systemic infection<sup>6,7,16</sup>. Vertical transmission has also been described in more than 20 children born to HIV-positive mothers<sup>21</sup>.

Systemic penicilliosis is an extremely rare disease in the non-immunocompromised host. Most of the patients have any form of immunodeficiency, acquired or iatrogenic. On the HIV-infected patients it is predominantly a late occurrence, with CD4 count normally around 50 cells/mm<sup>3,23</sup>.

Fever and weight loss are the most common first clinical manifestations, present in up to 95% of cases. Sometimes, prolonged fever is the only presenting symptom. Generalized lymphadenopathy and hepatomegaly were present in more than 60 to 80% of cases<sup>20</sup>. In both HIV-positive and HIV-negative patients the respiratory system is the most common organ affected at presentation<sup>5,19</sup>. Several clinical-radiological patterns have been described, the most common being the alveolar or interstitial infiltrates and the pleural effusions<sup>24</sup>. Cutaneous manifestations are frequent (up to 75% of cases) and are very important clues to the clinical diagnosis of penicilliosis. The majority of lesions are umbilicated papules (molluscum contagiosum-like). The lesions are mainly distributed on face and upper trunk.

*Penicillium marneffei* can be isolated from various clinical specimens by direct mycological examination or cultures. Specimens stained with Wright, Giemsa or Periodic Acid Schiff's show intracellular and extracellular basophilic, spherical, oval to elliptical, yeast-like organisms (3 ± 8 mm in diameter), with clear transverse section characteristic of *P. marneffei* yeast phase. Culture specimens from bone marrow aspiration and lymph nodes are the most sensitive (100%), followed by skin tissue (90%) and blood (76%), respectively<sup>20</sup>. In HIV-positive patients the fungemia seems to be more common than on HIV-negative patients especially in the context of AIDS patients of the Southeast Asia. The knowledge of this entity is far from complete: from its forms of infection to its best treatment, much has to be learned.

***Penicillium* spp infection other than *P. marneffei*:** *Penicillium* spp infection other than *P. marneffei* can cause a spectrum of clinical entities, being the superficial and allergic diseases far more common<sup>13</sup>.

Sensitization to *Penicillium* as well as other fungi is relatively common among asthmatics. Various sero-epidemiological studies conducted in several countries imply *Penicillium* as an environmental allergen of variable significance among asthmatic and atopic individuals<sup>13</sup>.

Superficial infections due to *Penicillium* spp include skin infections such as onychomycosis and dermatitis, eye infections such as fungal keratitis and conjunctivitis and otomycosis.

Invasive disease due to *Penicillium* sp other than *P. marneffei* is rare but does exist. Over the last 50 years, according to a recent review, a total of 34 cases of invasive infection have been described in the literature, most of them associated with non-immunocompromised hosts. Until now there have been descriptions of lung infection, endocarditis, peritonitis in CAPD, urinary tract, endophthalmitis, oesophagitis and intracranial infection<sup>13</sup>.

Regarding CNS infection, only three cases had already been reported, two of them in non-immunocompromised patients<sup>9,13,14</sup>. In the first case intracranial infection was the result of local spread from primary orbital-sinus infection causing a mycotic cerebral aneurysm and eosinophilic CSF pleocytosis. In the second case intracranial *Penicillium* infection followed primary lung involvement in a patient with acute leukemia. The third case has recently been reported and was the first to be the result of haematogenous dissemination in a non-immunocompromised patient. Treatment with amphotericin B and surgery failed to prevent death in the last two cases.

To our knowledge, this is the fourth documented case of CNS infection by a member of the *Penicillium* genera and the first one in Brazil.

## RESUMO

### Abscessos cerebrais múltiplos causados por infecção por *Penicillium* spp

Apresentamos um caso de infecção do sistema nervoso central (SNC) por *Penicillium* spp em paciente do sexo masculino, HIV-negativo no Brasil. O paciente apresentou-se ao Serviço de Urgência do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo queixando-se de alteração visual e dificuldade na fala. Exames de neuroimagem mostraram lesões múltiplas, compatíveis com abscessos. A biópsia esterotáxica revelou infecção fúngica, iniciando-se o tratamento com anfotericina B com sucesso inicial. O paciente morreu poucos dias depois, vítima de uma hemorragia digestiva maciça devido a varizes de esôfago. A necropsia e a análise microbiológica final da biópsia cerebral revelaram infecção por *Penicillium* spp. Existem centenas de espécies de fungos do gênero *Penicillium*. A peniciliose sistêmica é causada pelo *P. marneffe* e costumava ser uma doença rara, mas atualmente é uma das infecções oportunistas mais comuns em associação com AIDS no Sudeste Asiático. Infecção pelo *Penicillium* spp de espécie diferente do *P. marneffe* normalmente causa apenas doenças superficiais ou alérgicas mas doenças invasivas também ocorrem raramente. Nós relatamos o quarto caso de infecção do SNC por *Penicillium* spp.

## REFERENCES

- CAPPONI, M.; SEGRETAI, G. & SUREAU, P. - Pencilliose de *Rhizomys sinensis*. **Bull. Soc. Path. exot.**, 49: 418-421, 1956.
- COOPER, C.J. & MCGINNIS, M. - Pathology of *Penicillium marneffe*: an emerging acquired immunodeficiency syndrome-related pathogen. **Arch. Path. Lab. Med.**, 121: 798-804, 1997.
- DENG, Z.; RIBAS, J.; GIBSON, D. & CONNOR, D. - Infections caused by *Penicillium marneffe* in China and Southeast Asia: review of eighteen published cases and report of four more Chinese cases. **Rev. infect. Dis.**, 10: 640-652, 1988.
- DISALVO, A.; FICKLING, A. & AJELLO, L. - Infection caused by *Penicillium marneffe*: description of first natural infection in man. **Amer. J. clin. Path.**, 60: 259-263, 1973.
- DUONG, T. - Infection due to *Penicillium marneffe*, an emerging pathogen: review of 155 reported cases. **Clin. infect. Dis.**, 23: 125-130, 1996.
- HAMILTON, A.J.; JEAVONS, L.; YOUNGCHIM, S. & VANITTANAKOM, N. - Recognition of fibronectin by *Penicillium marneffe* conidia via a sialic acid-dependent process and its relationship to the interaction between conidia and laminin. **Infect. Immun.**, 67: 5200-5205, 1999.
- HAMILTON, A.J.; JEAVONS, L.; YOUNGCHIM, S.; VANITTANAKOM, N. & HAY, R.J. - Sialic acid-dependent recognition of laminin by conidia. **Infect. Immun.**, 66: 6024-6026, 1998.
- HILMARSDOTTIR, I.; MEYNARD, J.; ROGEAUX, O. *et al.* - Disseminated *Penicillium marneffe* infection associated with human immunodeficiency virus: a report of two cases and a review of 35 published cases. **J. Acquir. Immune Defic. Syndr.**, 6: 466-471, 1993.
- HUANG, S.N. - Acute disseminated penicilliosis. Report of a case and review of the pertinent literature. **Amer. J. clin. Path.**, 39: 167-174, 1963.
- IMWIDTHAYA, P. - Systemic fungal infections in Thailand. **J. med. vet. Mycol.**, 32: 395-399, 1994.
- IMWIDTHAYA, P. - Update of Penicilliosis marneffe in Thailand. **Mycopathologia (Den Haag)**, 127: 135-137, 1994.
- KOK, I.; VEENSTRA, J.; RIETRA, P.; DIRKS-GO, S.; BLAAUWGEERS, J. & WEIGEL, H. - Disseminated *Penicillium marneffe* infection as an imported disease in HIV-1 infected patients: description of two cases and a review of the literature. **Neth. J. Med.**, 44: 18-22, 1994.
- LYRATZOPOULOS, G.; ELLIS, S.; NERRINGER, R. & DENNING, D.W. - Invasive infection due to *Penicillium* species other than *P. marneffe*. **J. Infection**, 45: 184-207, 2002.
- MORRIS, F.H.; SPOCK, A. & DURHAM, N. - Intracranial aneurysm secondary to mycotic orbital and sinus infections. **Amer. J. Dis. Child.**, 119: 357-362, 1970.
- PANACKAL, A.A.; HAJJEH, R.A.; CETRON, M.S. & WARNOCK, D.W. - Fungal infections among returning travelers. **Clin. infect. Dis.**, 5: 1088-1095, 2002.
- RONGRUNGRUANG, Y. & LEVITZ, S.M. - Interactions of *Penicillium marneffe* with human leukocytes *in vitro*. **Infect. Immun.**, 67: 4732-4736, 1999.
- RUXRUNGTAM, K. & PHANUPHAK, P. - Update on HIV/AIDS in Thailand. **J. med. Assoc. Thai**, 84 (suppl. 1): S1-S17, 2001.
- SEGRETAI, G. - Description d'une nouvelle espece de *Penicillium*: *Penicillium marneffe*. **Bull. Soc. Mycol. France**, 75: 412-416, 1959.
- SEKHON, A.; STEIN, L.; GARG, A.; BLACK, W.; GLEZOS, J. & WONG, C. - Pulmonary Penicilliosis marneffe: report of the first imported case in Canada. **Mycopathologia (Den Haag)**, 128: 3-7, 1994.
- SIRISANTHANA, T. & SUPPARATPINYO, K. - Epidemiology and management of penicilliosis in human immunodeficiency virus-infected patients. **Int. J. infect. Dis.**, 3: 48-53, 1998.
- SIRISANTHANA, V. & SIRISANTHANA, T. - Disseminated *Penicillium marneffe* infection in human immunodeficiency virus-infected children. **Pediat. infect. Dis. J.**, 14: 935-940, 1995.
- SUPPARATPINYO, K.; KHAMWAN, C.; BAOSOUNG, V.; NELSON, K. & SIRISANTHANA, T. - Disseminated *Penicillium marneffe* infection in southeast Asia. **Lancet**, 344: 110-113, 1994.
- UNGPAKORN, R. - Cutaneous manifestations of *Penicillium marneffe* infection. **Curr. Opin. infect. Dis.**, 13: 129-134, 2000.
- WONG, S.S.; WONG, K.H.; HUI, W.T. *et al.* - Differences in clinical and laboratory diagnostic characteristics of penicilliosis marneffe in human immunodeficiency virus (HIV)- and non-HIV-infected patients. **J. clin. Microbiol.**, 39: 4535-4540, 2001.
- YOUSUKH, A.; JUTAVJITTUM, P.; PISETPOGNSA, P. *et al.* - Clinicopathologic study of hepatic *Penicillium marneffe* in Northern Thailand. **Arch. Path. Lab. Med.**, 128: 191-194, 2004.

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