Case report

Central nervous system infection due to *Penicillium chrysogenum*

Fallbericht. ZNS-Infektion durch *Penicillium chrysogenum*

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Summary

Penicillium chrysogenum was isolated from three subsequent cerebrospinal fluid (CSF) specimens of a 73-year-old male patient without immunological compromise. The isolated was tested against five antifungal agents according to the NCCLS M38-P macrodilution method. MICs were determined as follows: amphotericin B (AMB), 2 μg ml^{-1}; fluconazole (FLZ), 8 μg ml^{-1}; itraconazole (ITZ), 1 μg ml^{-1}; flucytosine (5FC), 0.125 μg ml^{-1}; and terbinafine (TRB), 0.06 μg ml^{-1}. The patient has been cured with FLZ.

Zusammenfassung

Aus drei aufeinanderfolgenden Liquorproben eines 73-jährigen Patienten ohne immunologische Defizite, aber mit neurologischen Symptomen, wurde *Penicillium chrysogenum* isoliert. Im Makrodilutionstest wurden folgende MHK-Werte bestimmt: Amphotericin B 2 μg ml^{-1}; Fluconazol 8 μg ml^{-1}; Itraconazol 1 μg ml^{-1}; Flucytosin 0.125 μg ml^{-1}; Terbinafin 0.06 μg ml^{-1}. Der Patient wurde erfolgreich mit Fluconazol behandelt.

Key words: *Penicillium chrysogenum*, penicillosis, central nervous system infection, traumatic implantation.

Schüsselwörter: *Penicillium chrysogenum*, penicillosis, ZNS-Infektion, Trauma.

Introduction

Penicillium is a very large genus, with about 200 distinguishable species.[1] In nature, penicillia are ubiquitous as saprobes on a wide diversity of materials. They are found in soil, on decaying vegetation, or on wood, while many species thrive in habitats with low water activity. Because of their dry, one-celled conidia they are airborne, and are therefore frequently encountered as laboratory contaminants. Most *Penicillium* species are hardly able to grow at 37 °C, and are unlikely to be aetiological agents of systemic mycosis.[2] The one exception is *P. marneffei*, which is endemic in Southeast Asia.[3] Hence, only a few cases of penicilliosis caused by non-*marneffei Penicillium* species have been reported to date. We present a case of central nervous system (CNS) penicilliosis caused by *P. chrysogenum* in an otherwise healthy white male.

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Case report

Clinical course

A 73-years-old male patient was admitted to the neurology department of Cerrahpasa Medical School Hospital in November 2001, because of a progressive weakness of the lower extremities and low back pain

radiating to the legs, which interfered with walking. He was a retired refuse collector. Three weeks before admission he experienced a subacute severe low back pain, which was rapidly progressing down both lower extremities followed by weakness and since then he was unable to walk. His pain was partly relieved with non-steroid anti-inflammatory drugs (NSAID) drugs and bed rest. He needed assistance in standing up. He was healthy until 1 year before when he experienced gradual unsteadiness and occasional seizures associated with action tremor of both hands and considerable slowness. Although Parkinson's disease was diagnosed and treatment was established, he discontinued his medication. He had been wounded 30 years ago by a trunk of electric fallen down on his head, which did not lead to loss of consciousness.

On admission, patient's physical examination was normal. His neurological examination revealed flaccid paraparesis with mild degree disuse atrophy, loss of deep tendon reflexes in the lower extremities and flexor plantar responses. Abdominal reflexes were lost on the right. There was no neck rigidity. Sensation for touch, pain and temperature were preserved. Vibration sense was lost bilaterally below trochanter major. Hoffmann sign was bilaterally positive and moderate rigidity on the arms was found. First interosseus atrophy of the hands was noted.

The opening pressure of the cerebrospinal fluid (CSF) (sample no. 1) on 23 November was normal and examination revealed 17 lymphocytes per ml and elevated protein level of 140 mg ml^{-1}, which triggered empiric treatment for tuberculosis. Because coccobacilli were reported by Gram staining of this first CSF specimen (no. 1) in bacteriological examination, the treatment switched to i.v. ceftriaxon 2×1 g day^{-1} empirically to cover possible chronic bacterial meningitis until the bacteriological culture of CSF would end, and discontinued 1 week later. On the second day of the antibiotic and antiparkinsonian treatment, he could be able to stand up without assistance. There was no growth on aerobic or anaerobic cultures of the first CSF specimen (no. 1). No mycological examination was performed in sample no. 1. CSF virology was negative as well as enzyme-linked immunosorbent assay (ELISA) tests for syphilis, toxoplasmosis, brucellosis and Lyme disease.

Lumbar puncture was repeated on 28 November (sample no. 2) and showed normal cell count and protein level in the second CSF specimen (no. 2) numerous fungal cells were observed; culture was positive for fungal growth. Oral treatment with fluconazole (FLZ) was started with 400 mg day^{-1} initial and 200 mg day^{-1} maintaining dose regarding to the antifungal susceptibility tests results of the isolated fungus. He remained on the antiparkinsonian treatment with 100/25 mg levodopa/benserazide t.i.d.

The third lumbar puncture was made on 5 December (sample no. 3) and similar *in vivo* fungal elements and *in vitro* macroscopical colony features were observed to the previous isolate, as did the last CSF specimen (sample no. 4) obtained on 12 December. Cranial, cervical, thoracic and lumbosacral spine magnetic resonance imaging showed normal results for his age with some degenerative changes of the spinal canal. Electrodiagnostic evaluation showed no denervation but neurogenic involvement of the muscles examined. The ENT consultation did not reveal any focus for fungal infection. Chest CAT-scan showed pleural calcification on the right diaphragmatic side and both hemithoraxes as well as pleuroparenchymal sequelae on the right apical segment.

The patient gradually started to walk with short step. When he was discharged, his pain was relieved, weakness was regressed to four of five and patella reflexes were returned. After discharge, FLZ was continued (200 mg day^{-1}) for about 4 months. Health progression was achieved, with the only problem remaining being standing up from a squat down position. On his last follow-up visit on October 2002, the patient was independent in his daily life. He was able to squat down and rise without assistance. He had mild degree parkinsonian features such as bilateral rest-tremor, rigidity and bradykinesia and his antiparkinsonian medication was adjusted.

Materials and methods

Isolation

The materials investigated were three successive CSF specimens (nos 2–4) of the patient. Specimen (no. 2) was centrifuged and the sediment was used for microscopical observation and culture. The sediment was stained with Gram, Ehrlich–Ziehl–Neelsen, Giemsa and India ink, and was plated onto Sabouraud glucose agar (SDA), brainheart infusion agar (BHIA), cooked sheep's blood agar (BA) and niger seed agar (NSA) and incubated at 25, 30 and 37 °C. The isolated fungus was transferred to malt extract agar (MEA), Czapek glucose agar (CDA) and brain heart-glucose-cysteine (BGC) agar. Identification was performed by morphological examination of slides in lactophenol cottonblue. The next CSF specimen (no. 3) was sent to deep mycosis laboratory within 6 days and the last (no. 4) after 2 weeks; all were examined similarly.

Molecular analysis

Sequences of the rDNA internal transcribed spacer (ITS1 and ITS2) region and β-tubulin were analysed to verify the species level identification of the isolate.

In vitro susceptibility testing

The MICs of five conventional antifungal agents for the case isolate were determined according to the NCCLS reference standard broth macrodilution method (M38-P) for filamentous fungi.[4] Isolate was subcultured onto potato glucose agar slant at 25 °C for 8 days. The inoculum was prepared by scraping the surface of the fungi with a sterile Pasteur pipette and directly suspending the fungal material in 5 ml of sterile distilled water. Conidial suspension was adjusted to 95% transmission at 530 nm, vortexed for 15 s, and diluted 1 : 100 in test medium to produce a final inoculum concentration of $4–5 \times 10^4$ cfu ml^{-1}. The following antifungal agents and ranges were used: amphotericin B (AMB; Bristol Meyers Squibb, Wallingford, CT, USA), 0.03–16 μg ml^{-1}; FLZ (Pfizer, Istanbul, Turkey), 0.125–64 μg ml^{-1}; itraconazole (ITZ; Janssen Pharmaceuticals, Beerse, Belgium), 0.03–16 μg ml^{-1}; fluorocytosine (5FC; Sigma, St Louis, MO, USA) 0.125–64 μg ml^{-1}; and terbinafine (TRB; Novartis, Basel, Switzerland), 0.03–128 μg ml^{-1}. Antifungal susceptibility testing was performed in Antibiotic Medium 3 (Oxoid, Hampshire, England) supplemented with 2% glucose and buffered with 0.165 mol l^{-1} morpholinepropanesulphonic acid (MOPS; Sigma) for AMB, and in RPMI-1640 (Sigma Chemical Co.) with L-glutamine but without sodium bicarbonate and supplemented with 2% glucose and buffered with 0.165 mol l^{-1} MOPS for the remaining antifungal agents. Tubes were incubated at 35 °C and read at 24 h interval when growth was observed in the drug-free control tube. MICs were determined by visual inspection after the control tubes showed appropriate growth. MIC end-points were determined as recommended by the NCCLS M38-P. For AMB, the MIC was defined as the lowest concentration of drug that completely inhibited growth that gave a score of 0 (optically clear). For other antifungals, the MIC was as the lowest concentration resulting in ≥50% inhibition of growth compared with that of untreated controls that gave a score of 2. *Paecilomyces variotii* ATCC 22319 was included as the quality control strain and was run in conjunction with the case isolate in the susceptibility test.[5–7]

Results

Mycology

Microscopical examination of CSF preparations (nos 2–4) revealed ovoidal to broadly ellipsoidal budding cells, chlamydospore-like cells with slightly verrucose walls, individual globose and elongated cells (Fig. 1a–d). Encapsulated yeast cells were not observed in India ink preparations.

Several colonies appeared on SDA after 7 days of incubation at 37 °C, which were powdery and folded, all on the striking line of the CSF specimen on the plate (Fig. 2a–d). The colonies were initially white and then

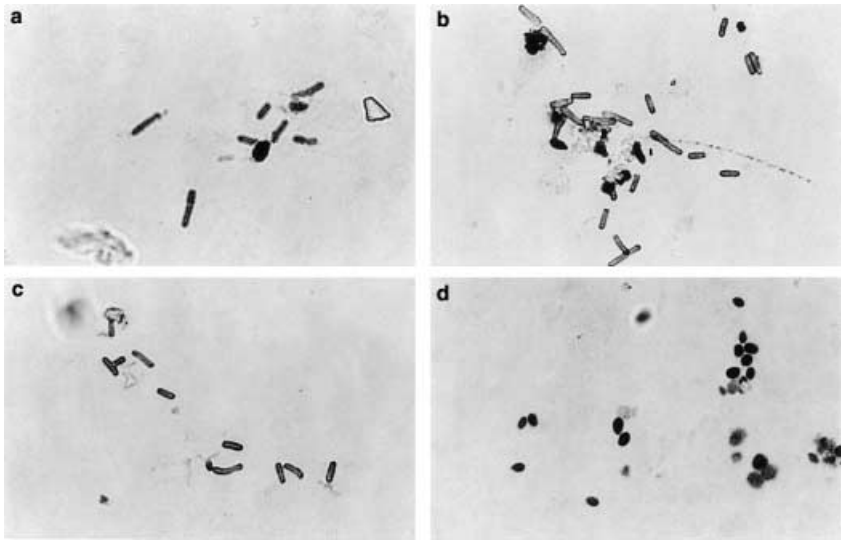

Figure 1 (a–d): Examples of *in vivo* morphology observed in cerebrospinal fluid (CSF) specimens (a–c: stained with Giemsa; d: stained with Ehrlich–Ziehl–Nielsen).

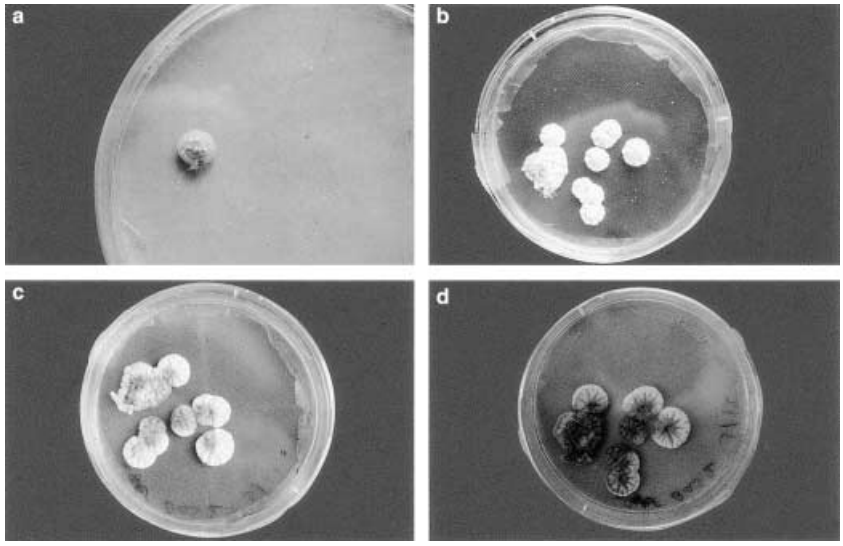

Figure 2 (a–d): Colonies growing on the Sabouraud glucose agar (SDA) plate.

became green with white periphery. No growth was observed on BHIA, BA and NSA. Colonies subcultured on CDA and MEA were powdery, folded, in green. The reverse of colonies was buff with no pigment production. Microscopic examination revealed hyaline hyphae and penicilli with abundant, green conidia. The same fungus was obtained from the second and third CSF specimens.

Molecular analysis

The isolate was identified as *P. chrysogenum* by morphological observation; the identity and verified by rDNA ITS1 and ITS2 sequences and tubulin comparing with data present in CBS. Its ITS sequence was 100% identical to that of CBS 306.48, the ex-type of *P. chrysogenum*. The strain was enlisted in the CBS culture collection as CBS 110824.

Antifungal susceptibility testing

The following MICs were determined as follows: AMB, 2 μg ml^{-1}; FLZ, 8 μg ml^{-1}; ITZ, 1 μg ml^{-1}; 5FC, 0.125 μg ml^{-1}; and TRB, 0.06 μg ml^{-1}.

Discussion

The common blue-green moulds of *Penicillium* are among the most abundant mesophilic airborne fungi in nature and in the human environment.[2,8] They are frequently encountered as laboratory contaminants. *Penicillium marneffei*, being unique among the members of *Penicillium* by its thermoregulated dimorphism, is the only species known to be a primary pathogen of humans and animals. At 37 °C *in vitro*, it produces slow growing, waxy colonies.[2,3,9,10] It is endemic to Southeast Asia.

Infection by other members of the genus *Penicillium* are very rare. Also *P. verruculosum*, once isolated from a case of osteomyelitis in a dog, exhibits good growth at 37 °C.[2] In contrast, most other species are unable to grow at 37 °C. Some cases of deep organ infections by thermo-intolerant species have nevertheless been reported. Among the aetiological agents were *P. brevicompactum, P. chrysogenum, P. citrinum, P. commune, P. decumbens*, isolated from human mycoses, and *P. griseofulvum* from a captive toucan.

General reviews of *Penicillium* pathology were published by Mori *et al.*,[11] Pitt,[12] de Hoog *et al.*[2] and Liratsopulos *et al.*[13] The first verified case of systemic penicillosis caused by non-*marneffei Penicillium* was reported in 1963 by Huang and Harris.[14] The patient had acute leukaemia and was treated with antibiotics and steroids. At autopsy, the patient was shown to have had disseminated cerebral and pulmonary penicillosis and gastrointestinal candidosis. Extensive growth of the fungus was evident in the patient's lung and brain, with vascular invasion, thrombosis and infarction of the lungs. The organism was identified as *P. commune*, an infrequently encountered soil saprobe.[1,12] *Penicillium chrysogenum* was implicated in cases of otomycoses, endophthalmitis, keratitis, endocarditis and a cutaneous infection. Data are summarized in Table 1, with accent on therapy. A fatal case of necrotizing oesophagitis in an AIDS patient, necrotizing pneumonia in a cancer patient and a systemic infection in an immunocompromised patient were also reported.[2] This spectrum of mycoses

Table 1 Review of reported human *Penicillium chrysogenum* infections.

Infection	Author (reference)	Age/sex	Underlying conditions	Treatment	Outcome
Endocarditis	Upshaw[27]	31/F	Aortic prosthesis		Died
Otomycosis	Yasin[28]				
Endophtalmitis	Eschete[29]	32/M	Trauma	AMB + natamycin	
Keratitis	Prasad[30]				
Necrotizing oesophagitis	Hoffman[15]	30/M	AIDS	AMB, KTZ	Died
Necrotizing pneumonia	d'Antonio[23]		Cancer	Lobectomy + ITZ	Cured
Systemic infection	Keung[31]		Immunocompromised, ALL		
Cutaneous infection	Lopez-Martinez[26]	M	None	ITZ	Cured
Cerebral infection	Lyratzopoulos[13]	51/M	None	AMB, AMB + 5FC	Died
CNS infection	This study	73/M	Trauma ?	FLZ	Cured

M, male; F, female; CNS, central nervous system; ALL, acute lymphoblastic leukemia.

caused by *P. chrysogenum* suggests a significant invasive potential of the species. It is able to grow at body temperature.[12] *Penicillium chrysogenum* was isolated from oesophagus biopsy material of a 30-years-old HIV-infected male patient.[15] He died despite of oral KTZ (200 mg b.d.) and AMB (40 mg $day^{-1} \times 30$ days) treatment. The clinical response to antifungal therapy of opportunistic fungal infections is associated with factors related to the host immune status and/or underlying disease rather than with antifungal susceptibility of the mould and pharmacokinetics of the therapeutic agent.[16,17] Lack of an appropriate cell-mediated immune response can both predispose to and result in perpetuation of the infection. Furthermore, oral absorption of KTZ varies among different individuals and there is also concern, based on experience with mice, the subsequent use of AMB may be antagonized.[18]

In a recently reported[13] cerebral involvement of *P. chrysogenum* in a 51-years-old Pakistani male patient without significant immune defect, liposomal AMB (Ambisome, Gilead Sciences, Foster City, CA, USA) at 4 mg kg^{-1} day^{-1} was administered initially. During the next 10 days the AMB dose was increased to 19 mg kg^{-1} day^{-1} and later 5FC was added at a dose of 2.5 g (6 h). Nevertheless the patient died nearly 4 weeks after biopsy. The treatment failure might be attributed to insufficient penetration of AMB into brain and CSF[18] and late diagnosis of *Penicillium* infection.

Our patient was an otherwise healthy old man with a history of severe trauma about 30 years ago. A wooden electricity pole had fallen on his head. We assume a connection between the head injury and the present infection. The possibility of traumatic intracerebral implantation of fungi was proven by Kim *et al.*,[19] and similar long incubation periods after traumatic implantation are known in agents of chromoblastomycosis.[20]

Although on the second day of the ceftriaxon therapy the patient was able to stand up without assistance and gradually started to walk with short step, this should be an occasional event because such a fast transmission and activity in CNS cannot be achieved within 24 h. It might be attributed to the positive response of the patient to the levodopa treatment. There was no growth on aerobic or anaerobic organisms in CSF specimens. We could not find any predisposing factors and underlying disease. Parkinsonism and polyradiculopathy might be a sequela of the CNS fungosis.

Antifungal susceptibility profiles of *P. chrysogenum* have not yet been determined because of the extreme rarity of infections by this species. *In vitro* MIC values obtained by using a standardized method of testing, can play an important role in the management of invasive fungal infections. MIC data also are essential to obtain population distribution profiles of MIC values. However, because of the large number of factors that can influence the success of antifungal therapy for a presumably susceptible isolate, a low MIC does not necessarily predict clinical success, while, conversely resistance *in vitro* often predicts therapeutic failure.

The MICs of the case isolate were determined by NCCL M38-P methodology as follows: AMB, 2 μg ml^{-1}; FLZ, 8 μg ml^{-1}; ITZ, 1 μg ml^{-1}; 5FC, 0.125 μg ml^{-1}; and TRB, 0.06 μg ml^{-1}. Patient was treated with FLZ, which penetrates into CSF and he responded well. Wildfeur *et al.*[21] reported relatively low *in vitro* MIC values for two *P. chrysogenum* strains: 0.195 and 0.391 against AMB, 0.003 against ITZ, 0.049 against KTZ, 0.49 and 0.195 against VRZ. They concluded that AMB, ITZ, KTZ and VRZ, a modified chemical structure of FLZ, showed good activity against these strains. Although the investigators used a different macrobroth dilution method (i.e. medium, drug dilution ranges, inoculum concentration, total testing volume and

probably reading criteria) and the MIC values are known to be strongly dependent on the testing methodology, it is obvious that their *P. chrysogenum* strains showed similar azole susceptibilities as found in our isolate.

In general the appropriate choice of drug for non-*marneffei Penicillium* infections has not yet been determined. Alvarez[22] reported a disseminated penicillosis successfully treated with AMB. d'Antonio *et al.*[23] reported a cases of necrotizing pneumonia treated with lobectomy and ITZ therapy. However, Mok *et al.*,[24] Horré *et al.*[25] and Liratsopulos *et al.*[13] reported cases where AMB therapy failed. Treatment with ITZ was successful in a case of cutaneous penicilliosis caused by *P. chrysogenum*.[26] Given the high *in vitro* susceptibility and the better absorption of FLZ, we regard this therapy as optimal and our patient cured with FLZ. The patient was followed during 1 year and was observed to improve considerably.

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