Voriconazole-Resistant *Penicillium oxalicum*: An Emerging Pathogen in Immunocompromised Hosts

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***Penicillium* species are rarely reported agents of infections in immunocompromised patients. We report 3 cases of invasive mycosis caused by voriconazole-resistant *Penicillium oxalicum* in patients with acute myeloid leukemia, diabetes mellitus, and chronic obstructive pulmonary disease, while on voriconazole therapy. *Penicillium oxalicum* has not been previously recognized as a cause of invasive mycoses.**

Keywords. immunocompromised; India; invasive; *Penicillium oxalicum*; posaconazole; voriconazole resistance.

Penicillium species are ubiquitously present in the environment and are usually considered as laboratory contaminants or non-pathogenic. Among *Penicillium* species *Penicillium marneffei* is the only dimorphic member, which is an established agent of invasive mycoses in immunocompromised and immunocompetent patients [1, 2]. However, invasive fungal infections due to *Penicillium* species other than *P marneffei* such as *Penicillium chrysogenum* [3, 4], *Penicillium citrinum* [5], *Penicillium decumbens* [3, 6], *Penicillium piceum* [7, 8], *Penicillium commune* [9], and *Penicillium purpurogenum* [3] have also been rarely reported. The reduced susceptibility of these species to voriconazole, which is often the first-line therapy for invasive mold infections, is particularly worrisome [10, 11]. In this study, we report 3 rare cases of opportunistic fungal infection caused by voriconazole-resistant *Penicillium oxalicum* in patients with acute myeloid leukemia (AML), diabetes mellitus (DM), and chronic obstructive pulmonary disease (COPD), while on voriconazole therapy for 3–6 weeks.

CASE REPORTS

Case 1

In August 2013, a 12-year-old girl from Nepal presented to the Rajiv Gandhi Cancer Institute with fever and ecchymosis for 1 month and abdominal pain for 5 days. Her physical examination, chest x-ray, and ultrasound of the abdomen were unremarkable. The hemoglobin (9.2 gm/dL), white blood cell count (1200/μL), and platelet count (7000/μL) prompted a bone marrow biopsy, which revealed AML without maturation (AML-M1). Induction chemotherapy was initiated as per UK-AML12 protocol. Cefoperazone-sulbactam, metronidazole, and linezolid were administered empirically. As her fever persisted on day 4, imipenem/cilastatin was administered until day 15 but she remained febrile. On day 17, computed tomography (CT) of the thorax showed bilateral ill-defined nodules (Figure 1A). However, sputum and blood cultures were negative for bacteria and fungi. A probability of invasive pulmonary aspergillosis (IPA) was considered, and oral voriconazole (6 mg/kg twice daily) was given for 3 weeks. Meanwhile, she received another induction regimen in September 2013, during her fever defervescence of 4 days. On day 18 of induction, she developed right subcostal pain. An ultrasound of the abdomen revealed multiple rim-enhancing foci in both lobes of the liver and spleen. Fine-needle aspiration (FNA) of the hepatic lesion showed periodic acid-Schiff (PAS) positive septate hyphae (Figure 1B), which on culture yielded *P. oxalicum* (accession number VPCI979/P/13) with high minimum inhibitory concentrations (MICs) of voriconazole. The treatment was changed to posaconazole oral suspension (200 mg thrice a day) based on results of antifungal susceptibility testing (AFST). Her fever subsided after 4 days of posaconazole. A repeat abdominal ultrasound after 2 weeks of therapy showed reduction in size and number of lesions. Similarly, a CT chest scan showed complete resolution of lesions. Posaconazole was continued for 6 weeks during which she received 2 consolidation-chemotherapy cycles with high-dose cytarabine and is presently doing well.

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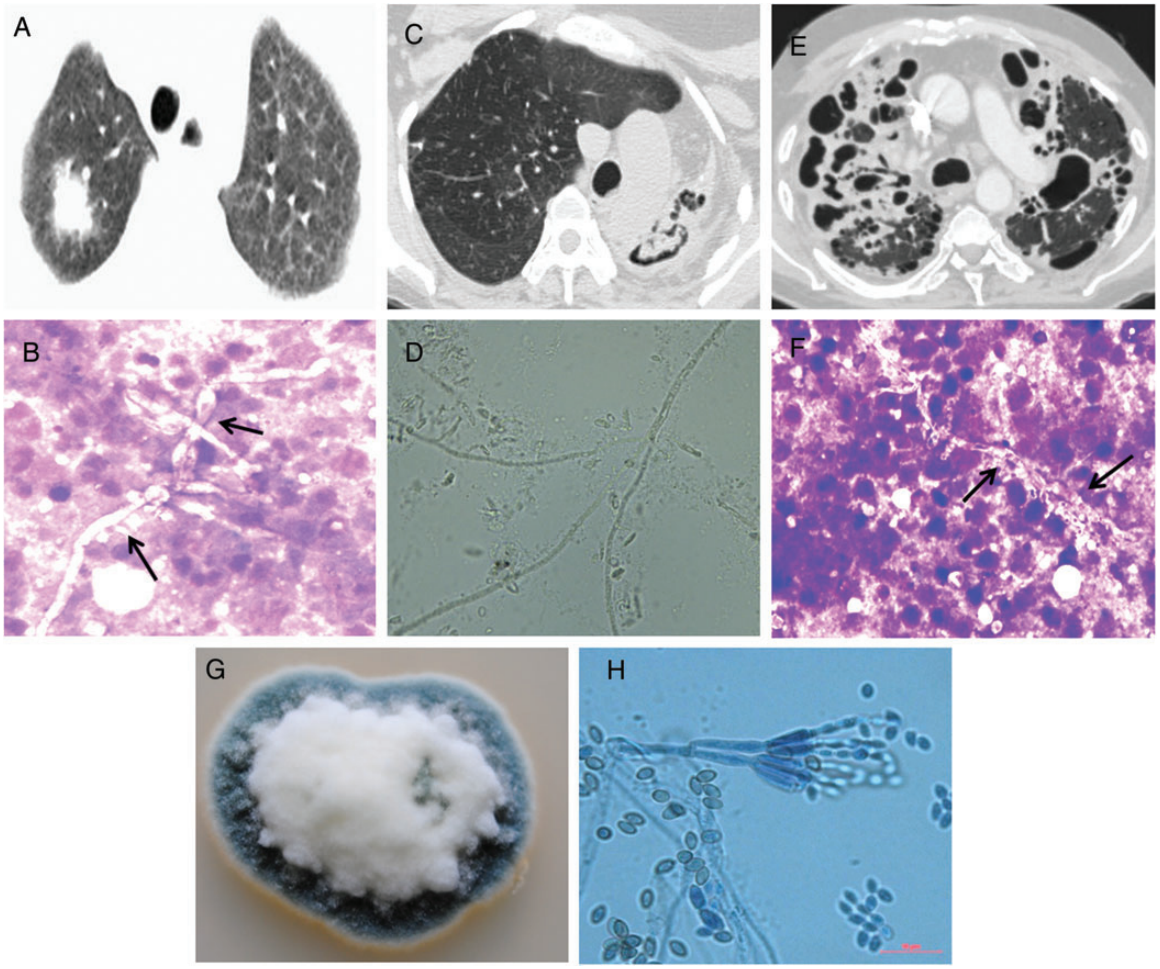

Figure 1. (A) Thoracic computed tomography (CT) of Case 1 showing an ill-defined nodule in the right upper lobe; (B) periodic acid-Schiff (PAS) stain of liver aspirate (Case 1) revealed septate hyphae, ×400; (C) thoracic CT of Case 2 showing an air-crescent within a cavitating nodule in the left upper lobe indicative of a mycetoma; (D) wet mount of KOH-digested fine-needle aspiration (FNA) of pulmonary lesion of Case 2 showed nondichotomously branching hyaline septate hyphae, ×400; (E) thoracic CT of Case 3 showing multiple thick-walled cavities along with bronchiectasis and pleural thickening in relation to the upper lobes bilaterally; (F) the FNA of a pulmonary nodule of Case 3 showed PAS-positive septate hyphae; (G) culture on Sabouraud's dextrose agar plates incubated at 28°C and 37°C showed bluish-green mold after 5 days of incubation; (H) lactophenol cotton blue mount of Czapek Yeast extract agar slide culture after 1 week of incubation revealed hyaline septate hyphae forming biverticillate conidiophores. The conidia were smooth to rough, globose to subglobose measuring 1.9 × 3.2 µm, ×1000.

Case 2

A 45-year-old female from Delhi, India was diagnosed with COPD, and she was treated with inhaled budesonide and formoterol and repeated systemic steroids for 3 years. She presented to the Vallabhbhai Patel Chest Institute, Delhi in October 2013 with complaints of productive cough, dyspnea, and intermittent fever. Her CT thorax revealed cavitating consolidation in the left upper lobe with mycetoma formation (Figure 1C), and sputum cultures yielded *Aspergillus fumigatus*. In addition, her serum was positive for precipitating antibodies against *A. fumigatus* [12]. A bronchoalveolar lavage (BAL) from the right upper lobe grew *A. fumigatus,* which was susceptible to azoles, but BAL galactomannan was negative. Chronic pulmonary aspergillosis (CPA) was diagnosed by compatible clinical symptoms, cavitating pulmonary lesions, precipitating antibodies, and the isolation of *A. fumigatus* from the BAL [13]. She received oral voriconazole (200 mg twice a day) for 59 days and showed initial symptomatic improvement which also corroborated with initial radiological and mycological clearance. However, on day 60 her complaints reoccurred. Thoracic CT revealed multiple cavitating nodules in the left upper lobe. A FNA from the pulmonary lesion showed nondichotomous septate hyphae in KOH mount (Figure 1D) and grew *P. oxalicum* (accession number VPCI533/P/12). No *Aspergillus* was isolated. Based on the results of AFST, oral posaconazole (200 mg thrice a day) was given for 6 weeks. She reported symptomatic relief, corroborated by replacement of the pulmonary nodules with fibrotic scars.

Table 1. In Vitro Antifungal Susceptibility Profile of 3 Strains of *Penicillium oxalicum* Isolated From Patients Whose Clinical Characteristics Are Detailed Below

Characteristics	Case 1, VPCI 979/P/13	Case 2, VPCI 533/P/12	Case 3, VPCI 1136/13
Age/Sex	12/F	45/F	54/M
Clinical summary	AML, on induction chemotherapy	COPD, on steroids	COPD, on steroids, uncontrolled diabetes mellitus
Present clinical diagnosis	Suspected pulmonary aspergillosis	CPA	CPA
VRC: indication	Empirical therapy for IPA	Therapy for CPA	Therapy for CPA
VRC: started after admission on day	17	12	7
Symptoms	Intermittent fever	Intermittent fever since 1.5 years, cough	Dyspnoea, anorexia, weight loss, intermittent fever since 4 years
Radiology	Nodule, upper lobe of right lung; enhancing ring lesions in liver and spleen	Diffuse, bilateral pulmonary infiltrates	Cavitating consolidation, middle lobe, lingual and bilateral upper lobes of the lung
Site of Infection	Liver, spleen and lung	Lung	Lung
Duration of VRC therapy (days)	38	59	49
Clinical specimen	Liver aspirate	FNAB, BAL, sputum	FNAB, sputum
In vitro AFST (MIC/MEC μg/mL)			
VRC	2	>16	2
AMB	≤0.03	0.5	0.5
ITC	0.5	2	1
POS	0.125	0.5	0.125
ISA	8	8	8
CAS	1	0.5	0.5
Treatment (duration)	POS (6 weeks)	POS (6 weeks)	Death before start of the therapy
Outcome	Survived	Survived	Death

Abbreviations: AFST, antifungal susceptibility testing; AMB, amphotericin B; AML, acute myeloid leukemia; BAL, bronchoalveolar lavage; CAS, caspofungin; COPD, chronic obstructive pulmonary disease; CPA, chronic pulmonary aspergillosis; FNAB, fine-needle aspiration biopsy; IPA, invasive pulmonary aspergillosis; ITC, itraconazole; MEC, minimum effective concentration; MIC, minimum inhibitory concentration; POS, posaconazole; ISA, isavuconazole; VRC, voriconazole.

Case 3

A 54-year-old male from Delhi was being treated with oral prednisolone and inhaled corticosteroids for COPD for 6 years. He presented to the Vallabhbhai Patel Chest Institute in November 2013 with dyspnea, anorexia, weight loss, and intermittent fever. He had poorly controlled DM type 2, for 7 years. His thoracic CT showed bilateral upper lobe cavities with pleural thickening (Figure 1E). Sputum cultures were negative for bacterial pathogens, but microscopy showed septate hyaline hyphae. Fungal culture grew *A. fumigatus*, which had a voriconazole MIC of 0.06 μg/mL. Serum was positive for precipitating antibodies against *A. fumigatus*, but galactomannan was negative [12, 13]. Chronic pulmonary aspergillosis was diagnosed and oral voriconazole (200 mg twice daily) was prescribed. After an initial improvement, his condition deteriorated on day 40, when he developed hemoptysis. The thoracic CT showed fresh nodules in the right middle and left lingular lobes, in addition to the above findings. Computed tomography-guided FNA from a right middle lobe nodule on day 45 was positive for septate hyphae (Figure 1F) and grew a pure culture of *P. oxalicum* (accession number VPCI1136/13). Unfortunately, on day 49 the patient succumbed to massive hemoptysis. A diagnosis of invasive pulmonary *P. oxalicum* infection was also established by culture of a post mortem lung biopsy.

Direct microscopy of KOH mounts of the liver (Case 1) and lung (Cases 2 and 3) aspirates showed hyaline, septate, nondichotomously branching hyphae, which were PAS positive. All of the specimens cultured on Sabouraud's dextrose agar plates, incubated at 28°C and 37°C, showed white cottony mold colonies after 2 days at both temperatures, which later turned bluish-green (Figure 1G). Lactophenol cotton blue mounts of Czapek Yeast extract agar (HiMedia Laboratories, Mumbai, India) slide culture after 1 week of incubation revealed hyaline septate hyphae forming symmetrical monoverticillate/biverticillate conidiophores with metulae in whorls of 3–5. Phialides were closely packed and ampulliform. The conidia were smooth to rough, globose to subglobose measuring 1.9 × 3.2 μm (Figure 1H). The identity of isolates was confirmed by partial sequencing of β-tubulin and calmodulin genes [14, 15]. The β-tubulin and calmodulin gene sequences exhibited 99% identity with *P. oxalicum* isolates from Korea, Malaysia, China, and the

Table 2. Global Literature Review of Invasive Cases due to *Penicillium* Species Other Than *Penicillium marneffei*

Year	Sex/Age (yrs)	Underlying Disease	Organ Involved	Organism and Identification	Diagnosis	Specimen Positive	Treatment and Outcome	In Vitro Susceptibility
1951–2000 [3] $N = 34$	22 M, 8 F, 4 unknown status	Immunocompromised ($n = 9$; includes 2 HIV, 5 acute leukemia, 1 chronic hemolytic anemia, 1 CGD]; immunocompetent ($n = 25$);	Heart, lung peritoneum, eye, brain, urinary tract, esophagus	*P. purpurogenum* ($n = 2$), *P. citrinum* ($n = 1$), *P. brevicompactum* ($n = 1$), *P. chrysogenum* ($n = 5$), *P. decumbens* ($n = 3$), *P. janthinellum* ($n = 1$), *P. lilanicum* ($n = 2$), *Penicillium* species ($n = 19$)	Pulmonary infection ($n = 13$), prosthetic valve endocarditis ($n = 4$), CAPD peritonitis ($n = 6$), endophthalmitis ($n = 5$), fungemia (1), esophagitis (1), upper UTI (1) and intracranial infection (2), paravertebral infection (1)	Lung biopsy, biopsy of cysts in corpus callosum, paravertebral soft-tissue biopsy[a]	Deaths (9), cured (18)	AMB, 0.25–4 μg/mL; FLU, 32–100 μg/mL; FC, 2–16 μg/mL; ITC, 0.03–0.5 μg/mL; KTC, 0.06 μg/mL[a]
2001 [8]	F/57	Cholangiocarcinoma	Disseminated	*P. piceum*, ITS sequencing	Fungemia	Blood	AMB for 2 weeks, but patient died of cardiovascular disorder	ND
2004 [22]	M/73	Trauma to the head leading to probable intracranial fungal implantation	Brain, spinal cord	*P. chrysogenum*, ITS and β-tubulin gene sequencing	CNS infection	CSF	FLU 400 mg/day and then 200 mg/day for 4 months	AMB, 2 μg/mL; FLU, 8 μg/mL; ITC, 1 μg/mL; 5-FC, 0.125 μg/mL; TERB, 0.06 μg/mL
2005 [23]	M/41	CLD	Brain	*Penicillium* species	Multiple brain abscess	Brain stereotactic biopsy	AMB began, but patient died due to gastrointestinal bleeding	ND
2005 [24]	F/51	Incarcerated peristomal hernia with perforated small bowel	Disseminated	*P. chrysogenum* identified by Southern Regional Research Centre (New Orleans, LA)	Disseminated penicilliosis	Blood	AMB and ITC and cured	AMB, 1.0 μg/mL; ITC, 0.25 μg/mL, VRC 1 μg/mL
2006 [7]	M/8	CGD	Lung	*P. piceum*, ITS sequencing	Pulmonary nodule and adjacent rib osteomyelitis	CT-FNAC and surgically resected lung and rib lesions	Surgical removal of lung nodule and rib lesion, AMB and VRC and cured after 1 year treatment	ND
2007 [25]	F/46	CAPD	Peritoneum	*Penicillium* species	Peritonitis	Peritoneal fluid	FLU and AMB, but patient died due to septicemia	ND

Table 2 continued.

Year	Sex/Age (yrs)	Underlying Disease	Organ Involved	Organism and Identification	Diagnosis	Specimen Positive	Treatment and Outcome	In Vitro Susceptibility
2013 [26]	M/78	History of bronchial asthma and pulmonary emphysema	Lung	*P. digitatum*, β-tubulin gene sequencing	Pneumonia with fungal ball	Sputum	ITC, MFG, VRC, AMB, and FLU, and patient died from renal failure	ND
2013 [27]	M/56	Lung transplant, immunosuppressive drugs received	Lung	*P. chrysogenum*, ITS and β -tubulin gene sequencing	IPM	BAL and transbronchial biopsy	VRC and CAS combination therapy; further AMB was added; patient died due to multiorgan failure and *Penicillium* infection	AMB, 16 μg/mL; VRC, 0.25 μg/mL; CAS, 0.19 μg/mL; POS, 0.25 μg/mL

Abbreviations: AMB, amphotericin B; BAL, bronchoalveolar lavage; CAPD, continuous ambulatory peritoneal dialysis; CAS, caspofungin; CGD, chronic granulomatous disease; CLD, chronic liver disease; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; FC, flucytosine; FLU, fluconazole; FNAC, fine-needle aspiration cytology; HIV, human immunodeficiency virus; IPM, invasive pulmonary mycosis; ITC, itraconazole; ITS, internal transcribed spacer; KTC, ketoconazole; MFG, micafungin; ND, ; POS, posaconazole; TERB, terbinafine; UTI, urinary tract infection; VRC, voriconazole; ND, no details available

[a] Details provided include 3 cases reported by Lyratzopoulos et al [3].

Netherlands (GenBank accession numbers KC344992, JF521520, AY678546, and JX141543, respectively). The β-tubulin and calmodulin gene sequences are submitted to GenBank under accession numbers KJ022632–KJ022634 and KJ022635–KJ022637, respectively. All of the isolates are deposited in the CBS-KNAW Fungal Biodiversity Centre (Utrecht, The Netherlands) under the accession numbers CBS 137558–CBS 137560. In vitro antifungal susceptibility was determined using the Clinical and Laboratory Standards Institute microbroth dilution method, following the M38-A2 guidelines [16]. The antifungals tested were amphotericin B (Sigma-Aldrich, St. Louis, MO), itraconazole (Lee Pharma, Hyderabad, India), voriconazole (Pfizer, Groton, CT), posaconazole (Merck, Whitehouse Station, NJ), isavuconazole (Basilea Pharmaceutica, Basel, Switzerland), and caspofungin (Merck). The isolates showed excellent activity to amphotericin B (MIC range, <0.03–0.5 μg/mL), posaconazole (MIC range, 0.125–0.5 μg/mL), itraconazole (MIC range, 0.5–2 μg/mL), and caspofungin (MIC range, 0.5–1 μg/mL). However, all 3 isolates had high MICs of voriconazole (MIC range, 2 – >16 μg/mL) and isavuconazole (8 μg/mL) (Table 1).

The phylogenetic tree of β-tubulin sequences using maximum-likelihood analyses with 2000 bootstrap simulations [17] revealed that our *P. oxalicum* isolates were genetically related to environmental isolates from South Africa (GenBank accession number JX091528), Korea (GenBank accession number JF521520), Japan (GenBank accession number AB849501), Malaysia (GenBank accession number KC344992), and the Netherlands (GenBank accession number KF499574, CBS301.97). The present isolates had 99.5%–100% similarity with each other and 97.9%–100% with those from other countries, thus indicating intraspecies genotypic variation amongst the *P. oxalicum* strains.

DISCUSSION

The cases presented herein highlight the potential pathogenic role of voriconazole-resistant *P. oxalicum* in immunocompromised hosts. All patients reported were predisposed to invasive fungal infections due to the presence of blood dyscrasias, cancer chemotherapy, prolonged steroid use, uncontrolled DM, and preexisting anatomical lung damage, each of which has been reported as an independent risk factor for invasive fungal disease [18, 19]. The lung was the portal of entry for this pathogen. The patient with AML (Case 1) was a case of invasive pulmonary infection due to voriconazole-resistant *P. oxalicum*, and she was initially misdiagnosed as possible IPA. Thus, she was administered voriconazole, leading to dissemination pending appropriate therapy. Notably, Cases 2 and 3 developed *P. oxalicum* infection while on voriconazole therapy for CPA. The initial favorable response in Case 2 can be attributed to the activity of voriconazole against the voriconazole-sensitive *A. fumigatus*,

resulting in breakthrough infection with voriconazole-resistant *P. oxalicum*. One may argue that the isolation of *A. fumigatus* from the subsequent samples could have been inhibited by previous use of voriconazole and that the isolation of *P. oxalicum* could be contamination. However, the clinico-radiologic worsening of patients while on voriconazole, isolation of *P. oxalicum* from otherwise sterile, deep-seated tissues with FNA, and the absence of other pathogens suggests a pathogenic role of this mold. In addition, it may be pointed out that, although therapeutic drug monitoring for azoles was not performed, the initial favorable response to voriconazole (Cases 2 and 3) and subsequently to posaconazole, suggests optimal dosing of the drug. Case 3 had a similar background to Case 2 but was more immunocompromised due to uncontrolled DM. The patient succumbed to autopsy-proven progressive fungal illness before appropriate therapy could be instituted. Therefore, the possibility of acquiring breakthrough infections while on voriconazole therapy was likely in both. In previous studies, breakthrough infections with voriconazole-resistant molds such as mucormycetes have been reported in patients with hematological malignancies on voriconazole treatment/prophylaxis [20].

Penicillium oxalicum, a plant pathogen [21], has not been previously recognized as an agent of invasive mycoses. In a previous study, Lyratzopoulos et al [3] reported 3 cases of invasive mycoses due to *Penicillium* species and reviewed an additional 31 cases of invasive infections caused by *Penicillium* species other than *P. marneffei* from 1951 to 2000. We discuss 11 additional cases of invasive disease, reported subsequent to 2001 including the present report (Table 2) [3, 7, 8, 22–27]. Of the 45 cases reported globally, 16 occurred in immunocompromised patients and 29 occurred in immunocompetent patients. Among 16 immunocompromised patients, 6 had hematological malignancies, 3 were on immunosuppressive drugs, 2 were human immunodeficiency virus positive, and another 2 had chronic granulomatous disease. Other conditions included 1 case each of chronic liver disease, chronic kidney disease, and DM. Although *Penicillium* species are considered rare fungal pathogens in patients with hematological malignancies, 2 species of *Penicillium*, namely *P. citrinum* and *P. purpurogenum*, and the present case of *P. oxalicum* have been associated with leukemias [3, 5, 8]. It is likely that infections caused by *Penicillium* species are usually overlooked or misdiagnosed as aspergillosis due to nonspecific clinical and radiological findings. Moreover, direct microscopic examination of both the genera shows similar hyaline septate hyphae. The pathogenic species such as *P. chrysogenum* [3, 4], *P. citrinum* [5], *P. decumbens* [3, 6], *P. piceum* [7, 8], *P. commune* [9], and *P. purpurogenum* [3], previously reported as agents of invasive infections, grow at 37°C, whereas the majority of common laboratory aerial contaminants grow below this temperature.

Furthermore, resistance to voriconazole and other azoles have been well documented in *A. fumigatus*, and similarly species of *Penicillum* exhibit reduced susceptibility to voriconazole and itraconazole [11, 29]. Therefore, the role of accurate molecular identification and AFST of *Penicillium* isolates especially from invasive cases can hardly be overemphasized. In the present study, phenotypic characteristics, partial β-tubulin region, and calmodulin gene sequencing were used for identification of the isolates. The internal transcribed spacer (ITS) region, which is accepted as primary fungal barcode, could not be amplified for these isolates in spite of repeated attempts. Many species in the genus *Penicillium* may not be unambiguously identified by ITS sequencing alone, and (partial) β-tubulin or calmodulin sequences may be required to ensure correct species identification [14].

In addition, this mold has never been isolated before, either from CPA or allergic bronchopulmonary aspergillosis patients of our institute or from patients with hematological malignancies from the cancer hospital. The observation of voriconazole-resistant fungal infection developing during receipt of voriconazole therapy underscores the need for diagnostic vigilance in immunocompromised patients.

Note

Potential conflict of interests. J. F. M. received grants from Astellas, Basilea, and Merck. He has been a consultant to Astellas, Basilea, and Merck and received speaker's fees from Merck and Gilead.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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