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NOVEL ID CASES

First Reported Case of Invasive Cutaneous *Penicillium cluniae* Infection in a Patient With Acute Myelogenous Leukemia: A Case Report and Literature Review

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Certain *Penicillium* species are emerging opportunistic pathogens. While these can be common causes of airborne contamination of clinical cultures, an increasing number of reports describe clinically significant disease in the immunocompromised population, particularly in patients with hematologic malignancy. The typical site of infection is respiratory, but disseminated infection is also reported with some frequency. Therefore, culture growth of *Penicillium* in respiratory and other clinical samples from immunocompromised patients requires thorough investigation with clinical correlation. Here we report a case of angioinvasive *Penicillium cluniae* infection of the right shin in a patient with acute myeloid leukemia and review reported cases of invasive *Penicillium* infection (excluding *Talaromyces marneffei*) in hematologic malignancy patients to characterize the emerging pathogen in this vulnerable population.

Keywords. leukemia; invasive fungal infection; lymphoma; *Penicillium*; transplant.

Penicillium is a genus of fungi consisting of >300 species that are ubiquitous, often found in soil, vegetation, air, and various food products [1]. The wide distribution of *Penicillium* species in the environment makes it a common airborne contaminant in culture specimens. *Talaromyces marneffei* previously belonged to the genus *Penicillium* and was the most common species in this genus responsible for clinical infection, which is often disseminated, manifesting with symptoms varying from skin lesions to respiratory failure and circulatory collapse [1]. Non-*marneffei* species are increasingly recognized as a rare cause of invasive infection, often in the immunosuppressed population, including those patients with hematologic malignancy, and less often in nonimmunosuppressed patients in association with instrumentation.

Patients with hematological malignancy are at increased risk of invasive fungal infection, with the highest rates of infection in patients with acute leukemia, where the incidence rates range from 10% to 25% in patients with acute myeloid leukemia (AML) and are as high as 6.5% in patients with acute lymphoblastic leukemia (ALL), based on microbiological data [2]. Within this population, important risk factors for invasive fungal infection include intensive cytotoxic chemotherapy and prolonged neutropenia. While the most common causes of invasive fungal infection in this population include *Candida* and *Aspergillus*, infections caused by other molds, including *Penicillium* species, occur and are clinically impactful, particularly in patients with acute leukemia [2–5].

Invasive infection due to *Penicillium* species (excluding those due to *Talaromyces*) is rare; however, opportunistic infections localized to the lungs and disseminated disease have been reported in vulnerable hosts and, in some cases, have been fatal. Because the growth of *Penicillium* in clinical culture samples is often due to culture contamination or colonization, thorough investigation with pathologic correlation is necessary to delineate invasive infection from culture contamination. Here we describe the first reported case of a localized invasive skin and soft tissue infection due to *Penicillium* species in an adult with acute myeloid leukemia.

CASE REPORT

A 52-year-old man with AML in remission presented 18 days after completing his second cycle of consolidation chemotherapy with high-dose cytarabine with fever, chills, and malaise, despite taking prophylactic ciprofloxacin, amoxicillin-clavulanate, and famciclovir. He was not taking antifungal prophylaxis before admission. He reported right shin pain, swelling, and redness, which he attributed to striking his leg on a boat trailer 5 days before admission. He denied other localizing symptoms.

Examination revealed a 3.0×3.5-centimeter erythematous to violaceous nodule with central ulceration, eschar, and surrounding erythema (Figure 1A). His white blood cell count was 0.13 K/μL, and his absolute neutrophil count was 0. He became neutropenic with an absolute neutrophil count <500 K/μL 12 days before presentation (6 days after completing

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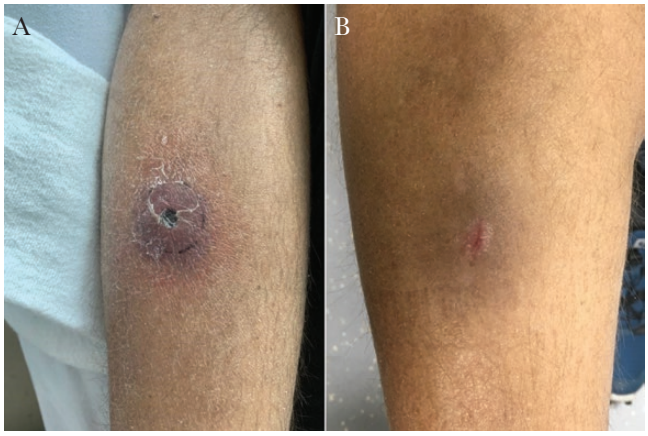

Figure 1. A, Right shin nodule with central eschar due to *Penicillium cluniae*. B, Right shin lesion after antifungal treatment for 4 months.

consolidation chemotherapy). A chest x-ray demonstrated no pulmonary opacities. He was treated with cefepime and vancomycin. One of 2 initial blood cultures grew *Staphylococcus haemolyticus*, which was believed to be a contaminant. All other blood cultures collected were negative. Serum 1-3-Beta-D glucan (Fungitell 1-3-Beta-D glucan assay, Associates of Cape Cod, East Falmouth, MA, USA) and galactomannan (Platelia Aspergillus Ag, Bio-rad, Hercules, CA, USA) tests returned negative/within normal limits. He continued to have fevers for 3 days, and the erythema around the skin nodule continued to expand.

Histologic examination of a punch biopsy of the right shin lesion demonstrated invasive, septate, fungal hyphae with acute-angle branching, forming a nodule of organisms in the interstitial and deep dermis (Figure 2). Subsequent tissue culture grew *Penicillium* species, which was later identified as *P. cluniae,* as described below (Figure 3).

Tissue from the patient's right shin was cultured following standard protocols. Cultures that were incubated on Sabouraud dextrose agar, inhibitory mold agar, brain heart infusion agar with cycloheximide and gentamicin, and blood agar plates at 30°C and 35°C resulted in a pure culture of mold with wooly, nearly circular, umbonate, radially and concentrically sulcate colonies within 1–2 days that were initially white but became gray-blue with a white margin upon maturation. The culture showed morphological features suggestive of *Penicillium* species. The isolate was sent to the Fungus Testing Laboratory at the University of Texas Health Science Center at San Antonio, Texas (FTL), for species identification and was accessioned as UTHSCSA DI21-110. The isolate was subcultured onto potato flakes agar and incubated at 25°C and 37°C, and a slide culture was also prepared.

Targeted sanger sequencing was performed for species identification as follows. Mycelial masses from the isolates were harvested from potato flake agar for DNA extraction, and genomic DNA was extracted. Partial beta tubulin (*BenA*) and calmodulin (*CaM*) genes were amplified and sequenced to compare with sequences of the same loci in previous studies. Polymerase chain reaction (PCR) and sequencing were carried out using the primer pairs Bt2a and Bt2b for *BenA*, and CF1 and CF4 for *CaM* [6, 7]. The generated sequences were used to perform BLASTn searches in GenBank [8]. BLASTn search results were considered significant with an E-value of 0.0 at 90%–100% identity and from 90% query coverage. Based on the BLASTn results, which were inconclusive, phylogenetic analyses were performed and included closely related Penicillium species. These were performed separately for each DNA locus and also with all loci combined. Sequences were aligned using MUSCLE as implemented in Sequencher, version 5.4.6, build 46289 (Gene Codes Corp. Ann Arbor, MI, USA) [9]. Substitution models were determined for each locus using the Model Finder program as implemented in IQ-Tree [10, 11]. Phylogenetic analyses using the maximum likelihood method based on the optimal evolutionary models for each locus and combined were conducted in IQ-Tree. The robustness of the phylogenetic trees was evaluated by 1000 bootstrap resampling using the Ultrafast Bootstrap Approximation in IQ-Tree, and Bayesian inference on the combined data set was conducted in MrBayes, version 3.2.5, using the previously determined optimal substitution model and the Markov chain Monte Carlo algorithm [12, 13]. The analysis stopped when the average standard deviation of split frequencies reached 0.01. The sample frequency was set at 100, and the first 25% of trees were removed as burn-in.

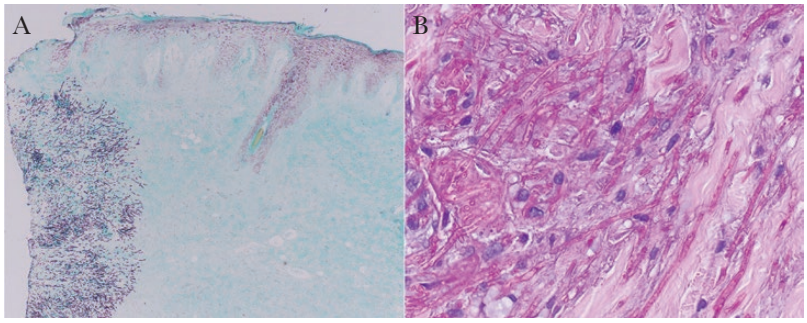

Figure 2. A nodule of delicate fungal elements is highlighted in the mid-dermis at the left edge of the biopsy using Gomori's methenamine silver stain (A). At higher magnification, a periodic acid Schiff with diastase stain reveals narrow, hyaline, fungal hyphae with frequent septations and predominantly acute-angle branching (B).

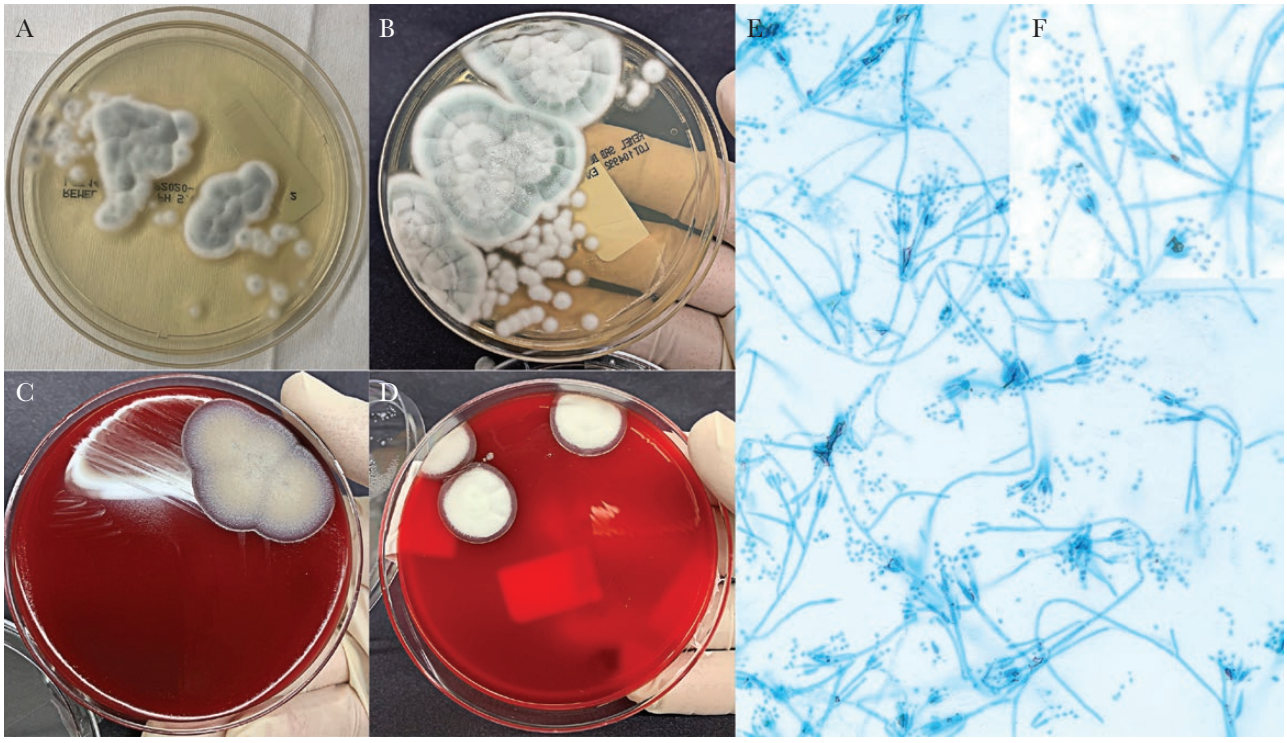

Figure 3. *Penicillium cluniae* was isolated from the skin biopsy tissue after incubation at 30°C and 35°C on sabouraud dextrose (A and B), inhibitory mold agar, brain heart infusion agar with cycloheximide and gentamicin (C), and sheep blood agar (D) plates. The mold inner surface became gray-blue upon maturation, with a white margin and light reverse (B). Lactophenol cotton blue stain revealed distinct microscopic features: long and thin regularly septate aerial hyphae, with monoverticillate to biverticillate branched "Penicillium-like" conidiophores (E). The conidiophores had smooth-walled long metulae and flask-shaped ampulliform phialides [2–4] with globose to subglobose (rarely ellipsoidal) conidia arranged in short chains (F).

The slide culture mount showed a *Penicillium* sp. with long regularly septate monoverticillate to biverticillate conidiophores with smooth metulae, typical of *Penicillium cluniae* [14].

BLASTn searches showed that isolate UTHSCSA DI21-110 is within the *Penicillium* subgenus *Aspergilloides*, section *Lanata-Divaricata*, series *Janthinella,* and 99%–100% identity with *Penicillium cluniae* CBS 326.89^{T} [15]. The best maximum likelihood trees from the individual loci and combined data sets showed isolate UTHSCSA DI21-110 clustered together with *Penicillium cluniae* at 1.00 Bayesian posterior probability value (PP)/99% bootstrap support (BS; *BenA*), 1.00 (PP)/100% BS (*CaM*), and 1.00 (PP)/100% BS (combined *BenA* and *CaM*), confirming its identification as *Penicillium cluniae* (GenBank Accession numbers *BenA* MW881270 and *CaM* MW881269) (Supplementary Figure 1).

In vitro antifungal susceptibility testing by Clinical and Laboratory Standards Institute (CLSI) broth microdilution methods demonstrated the following minimum inhibitory concentrations: amphotericin B at 0.5 µg/mL, isavuconazole at 1 µg/mL, micafungin at ≤0.015 µg/mL (minimum effective concentration), posaconazole at 0.25 µg/mL, terbinafine at 0.5 µg/mL, and voriconazole at 1 µg/mL [16]. Before the susceptibility results were available, the patient was treated with intravenous liposomal amphotericin B (5 mg/kg every 24 hours) and oral terbinafine (500 mg twice a day) and transitioned to oral posaconazole (300 mg daily) and terbinafine (500 mg twice a day) upon hospital discharge after neutrophil count recovery and resolution of fevers. Once susceptibilities were available, antifungal therapy was narrowed to posaconazole monotherapy. After 6 weeks of therapy, his shin lesion had almost completely resolved. After 4 months of therapy and an additional 2 cycles of consolidation chemotherapy, both of which caused >10 days of neutropenia each, only a small scar remained at the site of infection (Figure 1B).

DISCUSSION

Penicillium-like fungi are commonly recovered from clinical samples and in routine hospital airborne surveys, and they are often discounted as contaminants. In patients with hematologic malignancy, invasive fungal infection has an incidence rate as high as 25% and is an important cause of morbidity and mortality, with *Aspergillus* species representing the most frequently isolated microorganisms. *Penicillium* species (excluding *Talaromyces* species, such as *T. marneffei,* formerly known as *P. marneffei*) are a rare but increasingly recognized opportunistic pathogen causing invasive fungal infections in this population, particularly in patients with acute leukemia who are marrow suppressed from intensive chemotherapy [5, 17].

We performed a literature review of invasive *Penicillium* infection (excluding older identification of *P. marneffei*) among patients with hematologic malignancy reported in the English-language literature over the last 60 years. We identified a total of 11 cases of invasive *Penicillium* infection (Table 1). The median age was 19 years. Nine patients were being treated for acute leukemia, and 2 were transplant recipients (including 1 lung transplant recipient with T-cell lymphoma) at the time of diagnosis. Though the absolute neutrophil count was not available in some reports, neutropenia was common in the reports that provided this detail.

The majority of cases in this review were pulmonary [5, 18–23], including 1 that also caused local extension with pericardial tamponade [18], and 4 cases were disseminated infection [24–27]. These cases demonstrate that exposure to *Penicillium* via inhalation in vulnerable hosts appears to be a common mechanism leading to pulmonary and disseminated infection. Hesse et al. reported repeated growth of *P. citrinum* from bronchoalveolar lavage cultures in a hematopoietic cell transplant (HCT) recipient who was ultimately not found to have invasive pulmonary disease. The authors noted based on literature review of *P. citrinum* infection that the particularly profound level of immunocompromise associated with acute leukemia therapy may be necessary for invasive infection [17].

In contrast, isolated invasive skin infection, as we describe in the present case, has not been reported in this population. One case report describes multifocal cutaneous infection in a pediatric patient with AML with invasive *P. citrinum* in 2 anatomically distinct areas including the calf and hand after consolidation chemotherapy; however, pulmonary infection was also apparently present in this patient, who improved after treatment with caspofungin and itraconazole [24]. The mechanism of infection in the present case was likely cutaneous inoculation of an adult patient with underlying hematological malignancy and severe neutropenia, which led to local angioinvasion.

All cases in this review, included in Table 1, were proven based on European Organization for Research and Treatment of Cancer (EORTC) criteria [28]. Due to the ubiquity of *Penicillum* species in the environment, pathologic proof of invasive infection is necessary to make this diagnosis. Galactomannan reactivity has been reported in cases of invasive *Penicillium* infection and colonization [17, 21, 24]. Though several of the cases in this series were reported before 2003 when the galactomannan assay was commercialized, it is notable that among the 5 cases where serum or bronchoalveolar lavage samples were reported (including the present case), the test was positive in 2 cases. In addition, bronchoalveolar lavage galactomannan was also highly elevated in the case of *P. citrinum* pulmonary colonization reported by Hesse et al. in an HCT recipient, where the authors proved cross-reactivity of the BAL isolate with the assay [17]. In the present case, serum galactomannan and 1,3-beta-D-glucan were negative, which may reflect the low burden of infection posed by local cutaneous inoculation. The role of serum 1,3-beta-D-glucan in aiding diagnosis of invasive *Penicillium* infection is not clear. None of the cases reviewed here reported serum 1,3-beta-D-glucan results.

Multiple antifungal agents such as amphotericin B, itraconazole, voriconazole, caspofungin, and flucytosine have been used for variable periods of time to treat *Pencillium* infection. Guevera-Suarez et al. determined the antifungal susceptibility of 118 *Penicillium* isolates according to a CLSI broth microdilution M38 method for filamentous fungi. This study showed that terbinafine and echinocandins are highly active in vitro against *Penicillium* and *Talaromyces* spp. [29]. However, historically these antifungals are not widely used for treating invasive infections by these fungi. Amphotericin had intermediate antifungal activity, and azoles had variable activity against *Penicillium* species. *P. citrinum* and *P. oxalium,* in particular, demonstrated high minimum inhibitory concentrations to voriconazole, the first-line therapy for invasive aspergillosis [30]. Clinically, voriconazole's suboptimal antifungal activity for these species can pose a challenge for patients with acute leukemia, among whom *Aspergillus* is the most common cause of invasive pulmonary mold infection, and empirical therapy directed at radiographically noted pulmonary nodules is common [25]. The potential for some *Penicillium* species to cross-react with the galactomannan assay has the potential to further exacerbate this mismatch between empirical therapy choice and the antimicrobial spectrum of voriconazole in cases of invasive *Penicillium* infection [17, 24]. More data are needed from both in vitro susceptibility studies and clinical outcomes to determine effective treatment options for infections caused by *Penicillium*-like fungi. Performing in vitro susceptibility testing for clinical cases is key for individualizing care.

Notably, antifungal prophylaxis that is active against mold is not routinely used at our center after consolidation chemotherapy, as the strongest data supporting this practice are limited to the period of neutropenia following induction chemotherapy [31]. While it is possible that antifungal prophylaxis with an azole active against mold might prevent this type of infection, treatment with azoles can introduce complexity in the care of patients with hematologic malignancy due to drug interactions. Furthermore, some molds including some *Penicillium* species, as discussed above, are not universally susceptible mold-active azoles.

In conclusion, *Penicillium* is a rare cause of invasive infection in hematological malignancy, and one that requires careful clinical investigation to assess pathogenicity due to its abundance in the environment. Though exposure by inhalation leading to pulmonary infection appears to be the most common mechanism of infection in this population, we report a unique case of cutaneous infection after presumed skin inoculation. We conclude that diagnosis of invasive *Penicillium* infection requires growth of *Penicillium* in clinical cultures and histopathologic

Table 1. Proven Cases of Invasive *Penicillium* Infection in Patients With Hematological Malignancy Based on EORTC/MSG IFI Criteria

Ref	Age, Gender	Underlying Disease	Site of Infection	ANC	Organism	In Vitro Susceptibility (MIC)	Specimen	Galactomannan Antigen[c]	Treatment	Outcome
Huang et al., 1963	40 y, M	ALL	Disseminated (lung, CNS)	<500	*P. commune*	Not available	Lung and brain tissue from postmortem	N/A	None	Died from disseminated fungal infection
Mancao et al., 2003	17 y, M	ALL	Disseminated (liver, lung)	NR	*Penicillium* spp.	Not available	Liver FNA	NR	"Triple IV antifungal therapy"	Died from respiratory failure
Chowdhary et al., 2014	12 y, F	AML	Disseminated (lung, liver)	NR	*P. oxalicum*	AMB <0.03 μg/mL, VCZ 2 μg/mL, ITZ 0.5 μg/mL, ISA 8 μg/mL, PCZ 0.125 μg/mL, CSP 1 μg/mL	Liver FNA	NR	PCZ	Survived
Krishnan et al., 2015	2 y, M	AML	Disseminated (lung, skin)	NR	*P. citrinum*	Not available	Skin biopsy	Serum and BAL >10	CSP and ITZ	Survived
Mok et al., 1997	69 y, F	AML	Lung with pericardial extension	>500	*P. citrinum*	AMB, ITZ, FCZ, and 5-FC >32 μg/mL	Respiratory culture, autopsy	N/A	AMB and ITZ	Died from invasive fungal infection to pericardium, cardiac arrest
Mori et al., 1987	19 y, M	ALL	Lung	<500	*P. citrinum* and *Penicillium* spp.	AMB 12.5 μg/mL, MCZ 0.78 μg/mL	Lung tissue on postmortem	N/A	FLC, MCZ, and 5FC	Died from fungal infection–related pneumothorax
Shamberger et al., 1985	16 y, M	AML	Lung	<500	*Penicillium* spp.	Not available	Lobar lung resection	N/A	AMB and surgical resection	Survived
Shokouhi et al., 2016	44 y, M	AML	Lung	<500	*P. notatum*	Not available	Respiratory culture, lung biopsy	Serum 1.7, BAL negative	VRC	Survived
de la Cámara et al., 1996	21 y, F	ALL[a]	Lung	NR	*P. brevicompactum*	AMB 1.0 μg/mL, ITZ 0.5 μg/mL, 5-FC 16 μg/mL	Lung tissue from postmortem	N/A	AMB, 5-FC	Died, unknown cause
Ramirez et al., 2018	16 y, M	Lymphoblastic lymphoma[a]	Lung	NR	*Penicillium* spp.	AMB 1.0 μg/mL, ITZ 0.25, VCZ 1 μg/mL	Lung biopsy	BAL negative	AMB	Survived
Geltner et al., 2013	56 y, M	T-cell lymphoma[b]	Lung	NR	*P. chrysogenum*	AMB 16 μg/mL, VCZ 0.25 μg/mL, CSP 0.19 μg/mL, PCZ 0.25 μg/mL	Transbronchial lung biopsy	BAL negative	PCZ, CSP, AMB	Died of fungal pulmonary infection
Mehta et al., 2021	52 y, M	AML	Skin	0	*P. cluniae*	AMB 0.5 μg/mL, PCZ 0.25 μg/mL, TER 0.5 μg/mL	Skin biopsy	Serum negative	AMB, TER, PSZ	Survived

Abbreviations: 5-FC, 5-flucytosine; ALL, acute lymphoblastic leukemia; AMB, amphotericin B; AML, acute myeloblastic leukemia; ANC, absolute neutrophil count; BAL, bronchoalveolar lavage; CNS, central nervous system; CSP, caspofungin; EORTC, European Organization for Research and Treatment of Cancer; FLC, fluconazole; IFI, invasive fungal infection criteria; ISA, isavuconazole; ITZ, itraconazole; MCZ, miconazole; MSG, Mycoses Study Group; N/A, not applicable; NR, not reported; PCZ, posaconazole; TER, terbinafine; VRC, voriconazole.

[a]Bone marrow transplant recipient.

[b]Lung transplant recipient.

[c]Galactomannan assay became available outside of research in 2003, so it is not applicable for reports before then.

confirmation of invasive disease. In addition, antimicrobial susceptibilities are key to effectively guide treatment.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases online*. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Patient consent. The patient provided written consent. This report does not include elements that require approval from the local institutional review board.

Author contributions. All authors have reviewed the manuscript and contributed to writing, editing, and reviewing this case report.

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