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Disseminated Intravascular Infection Caused by *Paecilomyces variotii:* Case Report and Review of the Literature

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Paecilomyces variotii is a ubiquitous environmental saprophyte with worldwide distribution. Commonly found in soil and decomposing organic material [1, 2], *P. variotii* can also be isolated from drinking water [3] and indoor and outdoor air [4–6]. In immunocompetent hosts, *P. variotii* has been reported as a cause of locally invasive disease including prosthetic valve endocarditis [7, 8], endophthalmitis [9, 10], rhinosinusitis [11, 12], and dialysis-associated peritonitis [13, 14]. In contrast, disseminated infections are more commonly reported in immunocompromised patients, including those with chronic granulomatous disease [15], solid malignancy [16], acute leukemia [17], lymphoma [18], multiple myeloma [19], and after stem cell transplant for myelodysplasia [20]. In 1 case series examining invasive infections by non-*Aspergillus* molds, *P. variotii* was the most common cause after *Fusarium* spp. [21]. Here, we present the case of an immunocompetent patient with extensive intravascular infection involving prosthetic material. We describe successful induction therapy with combination antifungals and extended suppression with posaconazole with clinical quiescence and eventual normalization of serum fungal biomarkers.

Keywords. endovascular infection; endovascular mold; invasive mold; *Paecilomyces*.

CASE REPORT

A 60-year-old man presented with thoracic aortic dissection 7 years before this presentation. At the time of the dissection, he underwent repair of his ascending thoracic aorta with Hemashield graft and aortic valve resuspension; he was clinically well for the intervening 7 years. He then presented with left flank pain. Computed tomography angiogram (CTA) revealed left renal and splenic infarcts, which were felt to be the result of bland embolization originating from residual dissection flaps. He was discharged with anticoagulation.

He returned 2 months later with left arm numbness and weakness and was found to have occlusion of his left subclavian artery extending to the radial artery. He underwent extensive thromboembolectomy. The excised clot was felt to have an unusual appearance and was sent for routine bacterial culture and pathology. Findings on transthoracic echocardiogram and CTA were concerning for mural thrombus within the false lumen of the distal infrarenal abdominal aorta and adherent to the wall of the ascending aorta at the distal end of the aortic graft. Imaging also demonstrated evidence of mycotic pseudoaneurysms of the left subclavian and middle colic branch of the superior mesenteric artery and of multiple small cerebral mycotic aneurysms with punctate subacute right parietal and chronic right cerebral and precentral gyral infarcts. All of these findings raised concern for infection of his prosthetic aortic graft with septic embolization.

Aerobic and anaerobic cultures of the excised thrombus and routine blood cultures drawn at the time of his initial presentation all had no growth. Histopathology of both the brachial and radial portions of the thrombus revealed numerous fungal hyphal forms (Figure 1). Morphology was consistent with hyalophyphomycosis, as the fungal elements were septate and appeared nonmelanized when stained with hematoxylin and eosin. Both acute- and right-angle branching were present, with neither predominating, and numerous dilations (varicosities) of the hyphae were visible. The latter 2 features are uncommon in *Aspergillus* and raised the suspicion of a non-*Aspergillus* hyaline mold such as *Fusarium* or *Paecilomyces* or a dematiaceous mold with nonpigmented hyphae such as *Scedosporium*. Serum beta-D-glucan and galactomannan were both greater than the upper limit of quantification (Figure 2), supporting a diagnosis of extensive endovascular fungal disease.

Following the return of the pathology report from the excised thrombus, additional samples were taken from a necrotic,

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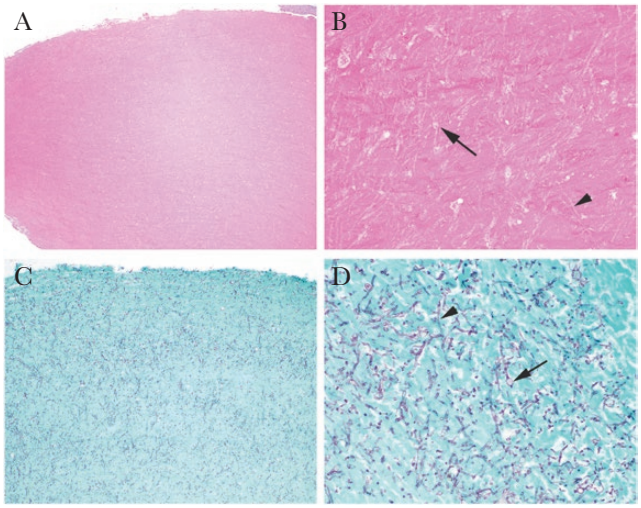

Figure 1. Histopathology from excised thrombus. A, B, Hematoxylin and eosin stain, 40× (A) and 400× (B). Numerous hyaline fungal hyphae are visible throughout the thrombus (arrowhead), some with varicosities (arrow). C, D, Gomori's methenamine silver stain, 100× (C) and 400× (D). This stain better highlights the abundant septate hyphae present (arrowhead), with occasional varicosities (arrow).

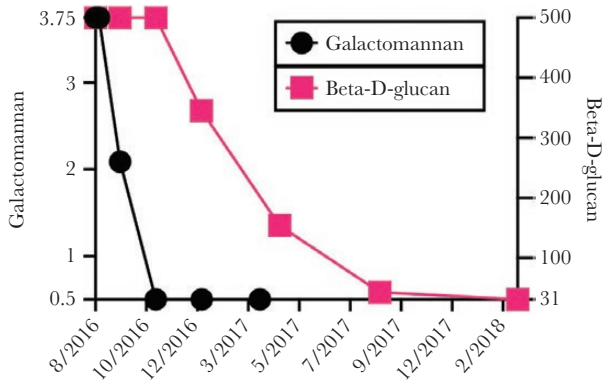

Figure 2. Serum fungal biomarkers over time. Galactomannan and beta-D-glucan were measured in peripheral blood over time after initiation of therapy. Galactomannan is reported as an index, with 3.75 being the assay maximum and 0.5 the lower limit of detection. Beta-D-glucan is reported in pg/mL.

possibly septic area of the left kidney and from a residual left upper extremity hematoma, but cultures including dedicated fungal cultures were negative. The paraffin-embedded, formalin-fixed pathology specimen of the excised thrombus was sent to the Department of Laboratory Medicine at the University of Washington for amplification and sequencing of 16S and 28S rDNA. No bacterial DNA was detected; sequencing of 28S rDNA identified *Paecilomyces variotii*.

After the renal and residual hematoma biopsies were obtained, liposomal amphotericin B 5 mg/kg/d was initiated pending sequencing results. After 4 days, in response to acute kidney injury, therapy was switched to micafungin 150 mg intravenously (IV) daily and voriconazole 300 mg twice daily (initially IV, then oral [PO]). When DNA sequencing results returned, given published data suggesting that posaconazole has more favorable in vitro activity against *P. variotii* [22, 23] voriconazole was stopped and delayed release posaconazole 300 mg PO daily was started. Micafungin was continued.

The patient was re-admitted the following month for ulnar neuropathy caused by brachial plexus compression, caused by enlargement of his left subclavian pseudoaneurysm. Posaconazole trough drawn at steady state was in the therapeutic range at 1300 ng/mL (serial levels in Table 2). Although beta-D-glucan levels were still greater than the upper limit of quantification, galactomannan had decreased to 2.1 (Figure 2). He underwent resection of the pseudoaneurysm, repaired with carotid-distal subclavian artery prosthetic bypass graft. The procedure was complicated by recurrent laryngeal nerve injury and left posterior cerebral artery stroke. When he presented for outpatient follow-up 2 months postprocedure, his resulting hoarseness had improved and he was recovering well from his right homonymous hemianopsia. In the setting of clinical improvement and undetectable galactomannan, micafungin was discontinued even though beta-D-glucan remained greater than assay.

On continued posaconazole therapy, he has achieved clinical stability. Acknowledging the difficulty in correlating serum fungal biomarker kinetics with clinical outcomes [24], we have nevertheless been reassured that his beta-D-glucan level gradually normalized (Figure 2). To date, he has received 40 months of posaconazole 300 mg daily, with plans for life-long suppressive therapy.

DISCUSSION

We present a case of disseminated intravascular infection with *P. variotii* in an immunocompetent host. *P. variotii* intraocular lens implant–associated endophthalmitis has been associated with operating room ventilation repairs [10]. We hypothesize that in the absence of any other predisposing factors, given this organism's environmental ubiquity [3–6], the patient may have been inoculated at the time that his endovascular graft was placed, with the long clinical latency explained by the organism's low virulence in an immunocompetent host. Discussion with infection control at the institution where the graft was placed did not reveal any additional cases.

Our case is also unusual in that the microbiologic diagnosis was made by 28S rDNA sequencing. A diagnosis of fungal infection was not suspected until the pathology resulted; thus the thrombus was not sent for directed culture at the time of thromboembolectomy. Although *P. variotii* can occasionally be cultured directly from the blood [18, 19, 21, 25], it did not grow in our case. Besides *Aspergillus* spp., the galactomannan assay is known to detect other closely related molds in the family Trichocomaceae, including *Paecilomyces* and *Penicillium* spp. [26, 27]. Galactomannan can also occasionally cross-react with more distantly related filamentous fungi such as *Fusarium* [28], as well as dimorphic fungi such as *Histoplasma* and

Table 1. ***Paecilomyces variotii*** **Infections With Treatment Outcomes**

Year	Infection	Organism Identification	Comorbidities	Treatment	Outcome
1963 [40]	Prosthetic mechanical mitral valve endocarditis complicated by septic emboli to spleen, kidneys, brain	Growth from blood cultures, identification on pathology	Rheumatic fever	Mycostatin 500 000 U Q6H	Treatment failure (death due to heart failure and lack of neurological improvement)
1974 [8]	Prosthetic mechanical aortic valve endocarditis	Growth from blood cultures, identification on pathology	Idiopathic severe aortic insufficiency	AMB 30–50 mg QD, 5FC 2.5 g QD (ultimately discontinued due to toxicity)	Treatment failure (death due to heart failure and septic cerebral emboli complicated by subarachnoid hemorrhage)
1981 [41]	Ventriculo-peritoneal shunt infection	Growth from CSF, identification on pathology of centrifuged CSF	Obstructive hydrocephalus due to basilar artery aneurysm, DM	Shunt exchange, intraperitoneal AMB 50 mg, then 100 mg	Treatment failure (hemorrhage leading to death)
1983 [42]	Pyelonephritis	Growth from stone sample	Nephrolithiasis	Uretero-lithotomy and antibacterials alone	Resolution
1984 [43]	Maxillary sinusitis	Growth from biopsy, identification on pathology	Recent endodontic treatment of tooth 25	Debridement alone	Resolution
1985 [44]	Pneumonia	Growth from bronchoscopy specimen	Hairy cell leukemia with distant steroids, chlorambucil, and cyclo-phosphamide followed by splenectomy	AMB 60 mg QD	Resolution
1988 [12]	Sphenoid sinusitis	Growth from sphenoidotomy specimen, identification on pathology		Debridement, 2 doses of AMB	Resolution
1991 [45]	Peritonitis complicated by fungemia	Growth from catheter tip, blood cultures	Chronic interstitial nephritis on PD	Catheter removal, AMB	Resolution (with transition to HD)
1991 [46]	Peritonitis	Growth from dialysate	Wilms' tumor with chemoradiation complicated by CKD on PD	FLC 6 mg/kg QD, then 3 mg/kg QD (failure) leading to catheter removal, AMB, FLC 3 mg/kg after TIW HD	Resolution with latter regimen (with transition to HD)
1992 [47]	Pneumonia	Growth from bronchoscopy specimen	DM	KTC 400 mg QD (failure) leading to AMB	Resolution with latter regimen
1992 [48]	Purulent cellulitis	Growth from debridement sample	Autosomal recessive CGD on IFN-γ	AMB 0.8 mg/kg/d for 7 wk, then ITC 100 mg BID for 1 y	Resolution
1993 [49]	Peritonitis (4 cases)	Growth from dialyate	PD	AMB intraperitoneal with failure leading to catheter removal in 2 cases, with 1 of those cases followed by total AMB 1480 mg over 4 wk; KTC 400 mg TID for 10 d, catheter removal in 1 case; KTC 200 mg QD with catheter removal in another	Resolution (with transition to HD) in all cases
1995 [50]	Chronic suppurative otitis media	Growth from biopsy specimen	Chronic amoebic dysentery	Debridement, KTC 200 mg PO QD for 1 mo, complicated by relapse, then topical KTC cream	Resolution
1995 [51]	Multifocal osteomyelitis, pneumonia	Growth from biopsy specimen	CGD	AMB 1.5 g/kg total dose, IFN-γ then ITC 200 mg QD for 1 y	Resolution
1995 [52]	Saline breast implant contamination	Growth from implant fluid		Implant removal without reimplantation	Resolution
1996 [14]	Peritonitis	Growth from dialysate	Hepatitis B, PD	Catheter removal, ITC and 5FC for 4 wk	Resolution (with resumption of PD)
1996 [53]	Deep SSI (complicating cesarean section)	Growth from percutaneous drainage fluid	Gestational diabetes	Debridement, antibacterials alone	Resolution
1996 [25]	Fungemia	Growth from blood cultures	Allogeneic BMT, CVC	CVC removal, AMB total of 641 mg, ITC 100 mg QD for 3 mo	Resolution
1998 [54]	Peritonitis	Growth from dialysate	Chronic pyelonephritis complicated by CKD on PD	AMB 1 mg/kg/d for total dose of 2500 mg IV followed by 1 mg/L IP, catheter removal, then ITC 400 mg QD for 5 wk, then ITC 200 mg QD for 11 mo	Resolution (with transition to HD)
1999 [9]	Endogenous endophthalmitis with altered mental status	Growth from vitreous aspirate	AML on cytotoxic chemotherapy	AMB (25 mg/d IV, intravitreal 5 mcg/d for 3 injections, topical 2% hourly), vitrectomy	Resolution (with preservation of remaining vision)

Table 1. Continued

Year	Infection	Organism Identification	Comorbidities	Treatment	Outcome
2000 [55]	Peritonitis	Growth from dialysate	14-mo-old with congenital bilateral renal hypoplasia on PD	FLC 5 mg/kg/d and 50 mg/L intraperitoneally for 4 wk	Resolution (with continuation on PD)
2002 [56]	Deep sternal SSI	Growth from sternal debridement tissue	Idiopathic bronchiectasis leading to bilateral lung transplantation	AMB for total dose of 1500 mg, debridement, then ITC 400 mg QD for 1 y	Resolution
2003 [16]	Meningo-encephalitis	Growth from CSF	Metastatic breast cancer on cytotoxic chemotherapy, DM	AMB 100, then 150, then 200 mg QD	Treatment failure (worsening mental status and gram-negative bacteremia leading to death)
2003 [57]	Peritonitis	Growth from dialysate	Hypertension and DM leading to CKD on PD	Catheter removal, AMB 50 mg QD, then ITC 200 mg QD	Treatment failure from progressive intraperitoneal presumed *P. variotii* and polymicrobial bacterial abscesses
2004 [10]	Exogenous endophthalmitis	Growth from vitrectomy specimen	DM, IOL for cataract	Vitrectomy, intravitreal AMB 5 mcg, KTC PO	Resolution (but with remaining visual acuity only finger counting at 2 m)
2005 [15]	Splenic abscess	Growth from abscess cultures	X-linked CGD	Drainage partial splenectomy, AMB 1–1.5 mg/kg/d for 1 wk then FLC 10 mg/kg/d, 5FC 100 mg/kg/d for 14 mo	Resolution
2005 [19]	Fungemia	Growth from blood cultures	MM leading to autologous BMT, CVC	AMB for 6 wk	Resolution
2005 [17]	Disseminated infection (fungemia, cellulitis, pneumonia)	Growth from blood cultures, identification on skin nodule pathology	ALL on chemotherapy, on VRC prophylaxis	AMB 5 mg/kg/d for 2 mo then ITC	Resolution
2007 [58]	Pyelonephritis	Growth from suprapubic urine culture and left ureteral stent	DM, nephrolithiasis with ureteral stents in place	AMB 1 mg/kg/d for 4 wk	Resolution
2010 [59]	Exogenous endophthalmitis		IOL for cataract	Intraocular corticosteroids and VRC	Resolution
2013 [60]	Pneumonia	Growth from broncho-alveolar lavage fluid	NHL treated with chemotherapy and allogeneic BMT complicated by presumed *Aspergillus* pneumonia, CMV esophagitis	AMB	Treatment failure (persistently elevated galactomannan with death from esophageal hemorrhage from CMV disease)
2013 [61]	Purulent nodular cellulitis	Growth from skin biopsy	DM	ITC 200 mg BID for 6 mo	Resolution
2014 [13]	Peritonitis (3 cases)	Growth from dialysate	PD, 1 also with DM	AMB in all cases (with 800 mg, 750 mg, 900 mg cumulative doses), additional ITC in 1 case	Resolution (but 1 with pneumonia leading to death and the others with transition to HD)
2015 [62]	Pneumonia	Growth from associated pleural effusions	DM	ITC 200 mg BID for 4 wk	Resolution
2015 [63]	Peritonitis	Growth from peritoneal fluid	Wison's disease necessitating liver transplant	AMB 3 mg/kg/d for 10 d combined with VRC 7 mg/kg BID (ultimately for 4 additional wk)	Resolution (with preservation of graft function)
2015 [64]	Peritonitis	Growth from dialysate	PD	AMB 1 mg/kg/d for 4 wk	Resolution (with continuation of PD)
2016 [11]	Pan-sinusitis	Growth from sinus tissue		Debridement, ITC 200 mg BID for 3 mo	Resolution
2016 [23]	Pneumonia	Growth from broncho-alveolar lavage fluid culture	AML treated with chemotherapy, haploidentical BMT	VRC (6 mg/kg BID then 4 mg/kg BID) with failure, then AMB (with infusion reaction), then POS 300 mg BID to QD	Resolution
2017 [65]	Peritonitis	Growth from dialysate	PD	AMB 3 mg/kg/d, ITC 400 mg QD for 4 wk	Resolution (with transition to HD)
2017 [18]	Fungemia	Growth from blood cultures	NHL, chemotherapy complicated by HBV reactivation and liver failure requiring transplant	AMB 5 mg/kg/d, VRC 200 mg BID for 8 d, then AFG 100 mg QD for 3 wk, then POS 200 mg suspension QID for 10 wk	Resolution
2018 [66]	Cutaneous ulcers	Growth from biopsy specimens	Renal transplant, DM	VRC	Resolution
2019 [67]	Pulmonary mycetoma	Growth from broncho-alveolar lavage fluid culture	Interstitial lung disease on prednisone	POS	Resolution (but with re-admission with presumed bacterial pneumonia leading to death)

Only reports with full-text articles available were included. Drug dosages were included when available.

Abbreviations: 5FC, flucytosine; AFG, anidulafungin; ALL, acute lymphocytic leukemia; AMB, amphotericin B; AML, acute myeloid leukemia; BID, twice daily; BMT, bone marrow transplant; CGD, chronic granulomatous disease; CKD, chronic kidney disease; CMV, cytomegalovirus; CSF, cerebrospinal fluid; CVC, central venous catheter; DM, diabetes mellitus; FLC, fluconazole; HD, hemodialysis; IFN-γ; interferon gamma; IOL, intraocular lens implantation; ITC, itraconazole; IV, intravenous; KTC, ketoconazole; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; PD, peritoneal dialysis; PO, oral; POS, posaconazole; QD, once per day; QID, four times daily; SSI, surgical site infection; TID, three times daily; TIW, three times weekly; VRC, voriconazole.

Table 2. Delayed-Release Posaconazole Therapeutic Drug Monitoring

Date	Dose	Level	Trough	Steady State
08/31/2016	300 mg daily	1570 ng/mL	Yes	Yes
09/09/2016	300 mg daily	1940 ng/mL	Yes	Yes
09/24/2016	300 mg daily	1300 ng/mL	Yes	Yes
10/04/2016	300 mg daily	3420 ng/mL	Yes	Yes
03/18/2017	300 mg daily	3630 ng/mL	Yes	Yes
08/29/2017	300 mg daily	2990 ng/mL	Yes	Yes

Blastomyces [26, 29]. Though we find it unlikely, it remains possible that our patient's infection was caused by a more fastidious galactomannan-positive mold that also responded to posaconazole, and the 28S result reflects environmental contamination of the pathology specimen. However, the referral lab that performed the PCR-based identification advised us that they have not previously identified *P. variotii* on PCR-based tissue testing, suggesting that this is not a common contaminant. Hopefully, as fungal DNA amplification and sequencing become more common, as available reference databases expand, and as protocols for DNA extraction become more standardized, there will be more data on the sensitivity and specificity of this approach. To aid in this endeavor, consensus definitions of invasive fungal infections have recently been updated to allow classification as "proven invasive mold infection" cases in which molds are seen on pathology and fungal DNA is successfully amplified [30].

Review of the literature is complicated by frequent microbiologic identification only to the genus level and previous taxonomic grouping of *P. variotii* with the generally more triazole-resistant (now *Purpureocillium*) *lilacinum* [31, 32]. Previous reports have mainly described treatment with amphotericin B formulations, often in combination with or with transition to an extended-spectrum triazole (Table 1). European guidelines endorse this practice [33], but in our case, kidney injury limited duration of liposomal amphotericin B therapy to 4 days. Though in vitro activity is difficult to correlate with clinical efficacy in non-*Aspergillus* mold infections [34] several in vitro studies of *P. variotii* have demonstrated low minimum inhibitory concentrations of echinocandins (with micafungin minimum inhibitory concentrations more favorable than those of caspofungin or anidulafungin) as well as triazoles (with posaconazole and itraconazole more active than voriconazole) [21, 35–38]. Data are scant for newer agents such as isavuconazole, but 1 study generated promising data for ibrexafungerp [35]. In vitro synergy has not been demonstrated between echinocandins and triazoles for *P. variotii* [36, 39] but given the extent of the infection and our inability to facilitate surgical debulking, our patient was initially treated with both micafungin and posaconazole. The patient remains well, now >3 years after transition to posaconazole monotherapy. His excellent outcome is striking in its contrast to those of patients with hematologic malignancy and non-*Aspergillus* mold infections [34] and perhaps reflects his preserved immune system more than the treatment strategy used.

Increasingly sophisticated molecular diagnostic approaches facilitate definitive organism identification for a growing number of unusual or difficult-to-diagnose infections. This increase in microbiologic diagnoses, in turn, offers the opportunity to expand our understanding of the spectrum of infections caused by individual organisms. Together with previously reported cases, our case suggests that *P. variotii* may have a predisposition for causing endovascular infection associated with prosthetic material in immunocompetent hosts. The case additionally illustrates that infection with low-virulence organisms can become extensive before causing symptoms that drive a clinical presentation. Failure to culture the organism despite a significant endovascular burden underlines the critical role that molecular diagnostics can play for both diagnosis and management. In this case, although our suspicion of fungal infection was very high based on pathology, sequencing results directed a change in antifungal agent. Our case additionally provides supportive evidence for the successful early use of posaconazole for endovascular *P. variotii* infection; given the substantial potential side effects of amphotericin formulations, an early change to alternate agents may have overall long-term benefit to patients.

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Potential conflicts of interest. J. A. B. reports receiving consulting fees from Roche Diagnostics, DiaSorin, Inc., and T2 Biosystems. M. B. B. reports being a stockholder of Pfizer Inc. A. K. B. reports being a co-inventor on US patent 9885088, Rapid phenotypic diagnosis of transcriptional expression signatures.

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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