

VALVULAR HEART DISEASE

CLINICAL CASE

Culture-Confirmed *Histoplasma* Endocarditis on Bioprosthetic Mitral Valve Managed Successfully Without Surgery



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ABSTRACT

BACKGROUND Prosthetic valve endocarditis due to *Histoplasma capsulatum* is exceedingly rare and difficult to diagnose.

CASE SUMMARY A 79-year-old man with a bioprosthetic mitral valve presented with subacute cognitive decline, pancytopenia, and hypercalcemia. He was afebrile and hemodynamically stable. Echocardiography showed vegetations on the valve. Initially, blood cultures were negative. Urine *Histoplasma* antigen and serum beta-D-glucan were positive, and fungal blood cultures later grew *H capsulatum* after 4 weeks of incubation. He was managed with liposomal amphotericin B followed by isavuconazole due to itraconazole contraindications. He gradually recovered without surgical intervention.

DISCUSSION This case illustrates the diagnostic and treatment complexities of *Histoplasma* endocarditis.

TAKE-HOME MESSAGES In endemic regions, consider *Histoplasma* in culture-negative prosthetic valve endocarditis. Early diagnosis may rely on beta-D-glucan and *H capsulatum* urine antigen before cultures become positive. Isavuconazole is a viable alternative when itraconazole is not an option. Selected patients can be managed successfully without surgery. (JACC Case Rep. 2025;30:105315) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

HISTORY OF PRESENTATION

A 79-year-old man with a bioprosthetic mitral valve presented to his cardiologist's office with progressive symptoms including altered mental status, worsening lower extremity swelling, fatigue, and poor appetite. His wife reported an insidious decline that had begun in the summer of the previous year,

characterized by gradual weight loss that had recently accelerated, along with intermittent night sweats and low-grade fevers.

Given his known history of ischemic heart disease and worsening heart failure symptoms, a cardiac catheterization was scheduled. However, baseline laboratory investigations revealed significant thrombocytopenia and hypercalcemia. Owing to

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ABBREVIATIONS AND ACRONYMS

ID = infectious diseases
PVE = prosthetic valve
endocarditis

these concerning findings, the procedure was deferred, and the patient was directly admitted to the hospital the same day for further management.

Review of systems revealed several weeks of stable exertional dyspnea and orthopnea. He had no chest pain, cough, palpitations, or epigastric pain. Rest of systems review was unremarkable. Physical examination showed bilateral leg edema. He was afebrile and hemodynamically stable and had no signs of systemic embolization.

PAST MEDICAL HISTORY

The patient was a lifelong farmer residing in Missouri, managing over 200 acres of farmland. He reported frequent tick bites owing to his outdoor occupational exposure and had regular contact with livestock, dogs, and cats. He had not sustained any recent animal bites. While he did not report direct

TAKE-HOME MESSAGES

- Consider *Histoplasma* in culture-negative PVE, particularly in patients with environmental exposures in endemic regions.
- Beta-D-glucan and *Histoplasma* urine antigen testing can provide rapid diagnostic clues before culture confirmation.
- Isavuconazole may be a well-tolerated treatment option in patients unable to use itraconazole.
- Surgical intervention is not always mandatory; selected patients may achieve favorable outcomes with medical therapy alone.

exposure to bird or bat droppings, his farming activities involved frequent soil contact, making such exposure highly probable in an endemic area. He had no known tuberculosis exposure or relevant travel

VISUAL SUMMARY Timeline of Illness, Diagnosis, and Management

Timeline	Major Updates
Before This Presentation	
22 y prior	• Coronary artery bypass graft surgery and coronary stent placement
21 y prior	• Coronary artery bypass graft re-do and bioprosthetic mitral valve placement
11 y prior	• Redo mitral valve replacement owing to torn leaflet
	• Four weeks postoperatively, the patient was hospitalized for 2 wk with acute fever, chills, and progressive dyspnea over preceding 2 wk
	◦ Imaging revealed patchy right-sided pulmonary infiltrates and moderate mediastinal lymphadenopathy
	◦ An extensive infectious diseases work-up, including blood cultures and echocardiography, was unrevealing
	◦ Respiratory cultures grew rare yeast, but this was not further characterized or investigated; at the time, clinical features did not point toward histoplasmosis, and targeted testing was not pursued
	◦ The patient was treated empirically with antibiotics
This Presentation	
Day 1	• The patient presented to his cardiologist with insidious symptoms, including worsening lower extremity edema, fatigue, and poor appetite
	• Cardiac catheterization was planned to rule out ischemia given the patient's strong history of ischemic heart disease; however, baseline laboratory tests revealed pancytopenia and hypercalcemia
	• The procedure was deferred, and the patient was directly admitted to the hospital for further evaluation and management
	◦ Hypercalcemia was managed acutely, with nephrology consultation
	◦ Hematology consultation for evaluation of pancytopenia
	◦ Cardiologists continued to provide ongoing inpatient follow-up
Day 2-3	• Calcium normalized with hydration, but the patient remained lethargic with episodes of delirium
Day 4	• Transthoracic echocardiogram revealed irregularly shaped echodensities on mitral valve chordae and bioprosthetic leaflets, raising suspicion for vegetations; other valves looked normal
Day 5	• Infectious diseases team consulted
	• Extensive work-up initiated, including blood cultures (with fungal cultures) and evaluation for causes of culture-negative endocarditis; screening for Whipple disease also ordered
	• Empirical antibiotics started: ceftriaxone and doxycycline
	• Transesophageal echocardiogram planned
Day 8	• Transesophageal echocardiogram confirmed vegetations on bioprosthetic mitral valve; there was mild regurgitation and moderate stenosis, with mean pressure gradient of 7 mm Hg at heart rate 83 beats/min; no paravalvular regurgitation was noted
	• Blood cultures remained negative; most of the infectious work-up was still pending
	• Antibiotics were continued, and vancomycin was added empirically
Day 9	• The patient remained afebrile but continued to have fluctuating mental status; blood cultures remained negative
	• Serum beta-D-glucan was positive, raising suspicion for fungal infection; periodic acid-Schiff staining of bone marrow was negative
	• Owing to persistent altered mentation, brain magnetic resonance was performed, which showed no evidence of an acute intracranial process

Continued on the next page

VISUAL SUMMARY Continued	
Timeline	Major Updates
Day 10	Urine <i>Histoplasma</i> antigen was reported positive
Day 11	- Liposomal amphotericin B (AmBisome) was initiated; vancomycin was discontinued - Continued ceftriaxone and doxycycline pending other laboratory tests
Day 15	- The patient showed some signs of improvement, appetite better, working with physical therapy - Blood cultures still negative; Most of infectious diseases work-up unrevealing - No change in management
Day 17	- The patient showed modest clinical improvement, though overall prognosis remained guarded - Blood cultures still negative - Continued AmBisome and ceftriaxone; doxycycline discontinued
Day 22	- The patient developed notable lower extremity edema, attributed to volume overload from pre- and post-saline infusions administered with AmBisome - Blood cultures remained negative - AmBisome and ceftriaxone were continued - Intravenous furosemide was initiated as needed, and frequency of saline infusions was reduced to manage fluid balance
Day 27	- The patient experienced increased shortness of breath despite furosemide therapy and reduction in saline infusions - Final dose of AmBisome was administered
Day 28	- Blood cultures still negative - AmBisome discontinued, and itraconazole started - Ceftriaxone continued
Day 30	- The patient was unable to tolerate itraconazole, and there were concerns regarding potential drug-drug interactions with other medications - The patient also reported a cough with thick sputum production - Blood cultures continued to remain negative - Itraconazole was switched to isavuconazole for antifungal therapy - Ceftriaxone was switched to piperacillin-tazobactam (Zosyn) to broaden antibiotic coverage
Day 31	On day 27 of incubation, fungal blood cultures were reported to be growing an organism
Day 32	- Follow-up TEE done, showing a 2.2 × 1.0 cm nonmobile thrombus adherent in the left atrium; the vegetation was not worse, and there was not any new valvular dysfunction - Apixaban was initiated; isavuconazole and Zosyn were continued
Day 38	- Zosyn was discontinued; isavuconazole was continued - Discharge planning started
Day 43	- Discharged to skilled nursing facility - Isavuconazole continued
Day 52	On day 46 of incubation, the fungal culture was isolated to be <i>Histoplasma capsulatum</i> complex
Wk 4 and 12 post-hospital discharge	- The patient was seen in outpatient follow-up; he continued to improve and was doing fairly well overall - Serum calcium remained normal without active treatment; pancytopenia persisted but stable - Follow-up chest computed tomography scan at wk 12 showed complete resolution of left-sided pleural effusion and partial improvement of right upper lobe mass - The patient continued lifelong isavuconazole therapy - Ongoing follow-up was arranged with infectious diseases physician, pulmonologist, cardiologist, and primary care physician

history. He was a former smoker and alcohol user, but denied any history of recreational drug use.

He had a complex cardiac surgical history, beginning with coronary artery bypass graft surgery and coronary stent placement 22 years prior. This was followed by redo coronary artery bypass graft surgery and bioprosthetic mitral valve replacement a year later. Ten years after that, he underwent a redo mitral valve replacement owing to a torn leaflet of the bioprosthetic valve. Approximately 1 month following the redo mitral valve replacement, the patient was hospitalized for 2 weeks after he presented with a 1-day history of fever and chills and 2 weeks of progressive dyspnea. Imaging revealed right-sided patchy pulmonary infiltrates and moderate mediastinal lymphadenopathy. Laboratory work-up was notable for thrombocytopenia and transaminitis. An extensive infectious diseases (ID) work-up,

including blood cultures and echocardiography, was unrevealing. Respiratory cultures grew a rare yeast, which was not further characterized. The patient was treated empirically with antibiotics, including doxycycline. He showed clinical and radiologic improvement, with near-resolution of infiltrates by hospital day 10. The diagnosis was a probable community-acquired pneumonia; however, in retrospect, this presentation may have represented an acute, self-limited pulmonary histoplasmosis infection.

Additional comorbidities included nonischemic cardiomyopathy, paroxysmal atrial fibrillation, chronic obstructive pulmonary disease, a benign pulmonary nodule, type 2 diabetes mellitus, hypertension, hypercholesterolemia, and compensated liver cirrhosis. He also had a recent untreated diagnosis of localized prostate cancer without metastasis.

TABLE 1 Initial and Follow-Up Laboratory Results

Laboratory Test	Reference Ranges	Results	
		On Admission	Week 12 Post-Discharge ^a
White blood count, cells/ μ L	4,300-10,000	3,100	2,900
Hemoglobin, g/dL	13.6-16.5	12.5	12.4
MCV, fL	82.0-99.0	88.6	98.2
Platelets, cells/ μ L	140,000-350,000	72,000	100,000
Sodium, mmol/L	137-145	134	134
Potassium, mmol/L	3.4-5.1	3.6	4.5
Magnesium, mg/dL	1.6-2.6	1.7	—
Chloride, mmol/L	98-107	99	102
Carbon dioxide, mmol/L	22-30	32	26
Blood urea nitrogen, mg/dL	9-20	31	31
Creatinine, mg/dL	0.7-1.30	0.87	1.17
Glucose, mg/dL	74-106	118	109
Calcium, mg/dL	8.4-10.2	12.6	9.3
Ionized calcium, mg/dL	4.6-5.1	6.6	—
Albumin, mg/dL	3.5-5.0	3.4	3.9
Alanine aminotransferase, U/L	<50	40	52
Aspartate aminotransferase, U/L	14-54	54	61
Alkaline phosphatase, U/L	38-126	165	169
Total bilirubin, mg/dL	0.2-1.3	1.5	1
NT-proBNP, pg/mL		5,530	3,420
Hemoglobin A _{1c} , %	<5.6%	6.1	—
Thyroid-stimulating hormone, μ IU/mL	0.47-4.68	3.49	—
Parathyroid hormone, intact, pg/mL	15-83	79	—
Total 25-hydroxyvitamin D, ng/mL	30-100	35	—
Prothrombin time, s	11.9-14.7	24.6	—
INR	0.9-1.1	2.2	—
Prostate-specific antigen, ng/mL	<3.9	0.1	—
Bone marrow analysis		Mildly hypercellular marrow with morphologically normal trilineage hematopoiesis	—
Bone marrow FISH			
Chromosome 8 and 20 5q-/-5/+5 tricolor, 7q-/-7 tricolor, KMT2A (MLL)(11q23)		Not detected	—
13q-/-13, 1p32/1q2, p53 (17p13.1)/NF1(17q11), CCND1/IgH t(11; 14), FGFR3/IgH t(4; 14), IgH/MAF t(14; 16), IgH/MAFB t(14; 20)		Not detected	—

Initial results demonstrated leukopenia, anemia, thrombocytopenia, hypercalcemia, and elevated NT-proBNP, whereas most other parameters were within normal limits. Follow-up results showed persistent but stable leukopenia, anemia, and thrombocytopenia; normalization of serum calcium levels; and improvement in NT-proBNP levels.

^aDash indicates test was not repeated.

FISH = fluorescence in situ hybridization; INR = international normalized ratio; MCV = mean corpuscular volume; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

About 5 days before this presentation, he had presented to another hospital due to weakness and a fall, and an antibiotic was initiated for a probable underlying bacterial infection. His medications included aspirin, atorvastatin, carvedilol, warfarin, finasteride, furosemide, glimepiride, metformin, tamsulosin, and recently initiated cefdinir.

DIFFERENTIAL DIAGNOSIS

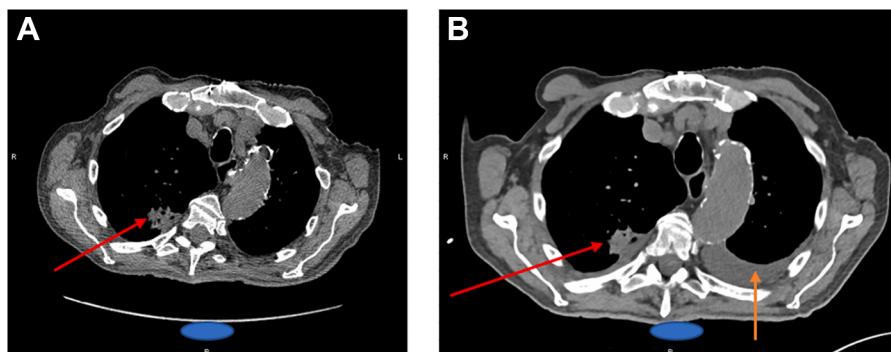
Given the subacute cognitive decline, fatigue, anorexia, weight loss, bilateral lower extremity edema, and exertional dyspnea—along with initial laboratory results showing pancytopenia and hypercalcemia in the context of a bioprosthetic mitral

valve and known ischemic heart disease—heart failure, prosthetic valve endocarditis (PVE), bone marrow malignancy, and granulomatous lung disease were differential diagnoses.

INVESTIGATIONS

Laboratory results (Table 1) were significant for pancytopenia (white blood cells 3,100/ μ L, hemoglobin 12.5 g/dL, and platelet count 72,000/ μ L), hypercalcemia (12.6 mg/dL), and elevated pro-B-type natriuretic peptide (5,530 pg/mL). Urinalysis was normal. Electrocardiogram showed rate-controlled atrial fibrillation with no acute changes. Computed tomography scan of the chest, abdomen, and pelvis revealed

FIGURE 1 Interval Radiologic Changes After Treatment



Serial chest computed tomography scan findings showing partial improvement of the right upper lobe mass (red arrows) and complete resolution of the left-sided pleural effusion (orange arrow) at 12 weeks post-discharge (A) compared with initial presentation (B).

a 3.0×2.1 cm right upper lobe lesion unchanged from previous studies, with mild lymphadenopathy and small bilateral pleural effusions (Figure 1).

MANAGEMENT

Hydration improved the hypercalcemia, but the patient remained lethargic and intermittently delirious. On hospital day 4, transthoracic echocardiography showed possible vegetations, prompting an ID consultation. Transesophageal echocardiography confirmed the vegetations (Videos 1 and 2), with a portion of the vegetation prolapsing into the left atrium that measured 1.3×0.6 cm (Figure 2). There was mild valvular regurgitation and moderate stenosis with a mean pressure gradient of 7 mm Hg at a heart rate of 83 beats/min. There was no paravalvular regurgitation. No vegetations were noted on other valves.

The ID team ordered an extensive work-up including blood cultures and fungal studies (Table 2) and initiated broad-spectrum antibiotics that included doxycycline to cover atypical organisms. Serum beta-D-glucan and *Histoplasma* urine antigen were both positive. After about 4 weeks of blood culture incubation, it started growing a fungus, which was later (in week 6) isolated to be *Histoplasma capsulatum*, confirming the diagnosis.

The patient was treated with liposomal amphotericin B (Ambisome; Gilead Sciences, Inc) for 17 days. It was discontinued after the patient developed signs of volume overload from the pre- and post-Ambisome saline hydration despite diuretics. He was transitioned to itraconazole, but developed intolerance. There were also concerns for significant drug-drug

interactions with the other medicines. Based on a combination of better tolerability, drug interaction profile, and clinical suitability,^{1,2} itraconazole was switched to isavuconazole, which he tolerated well.

OUTCOME

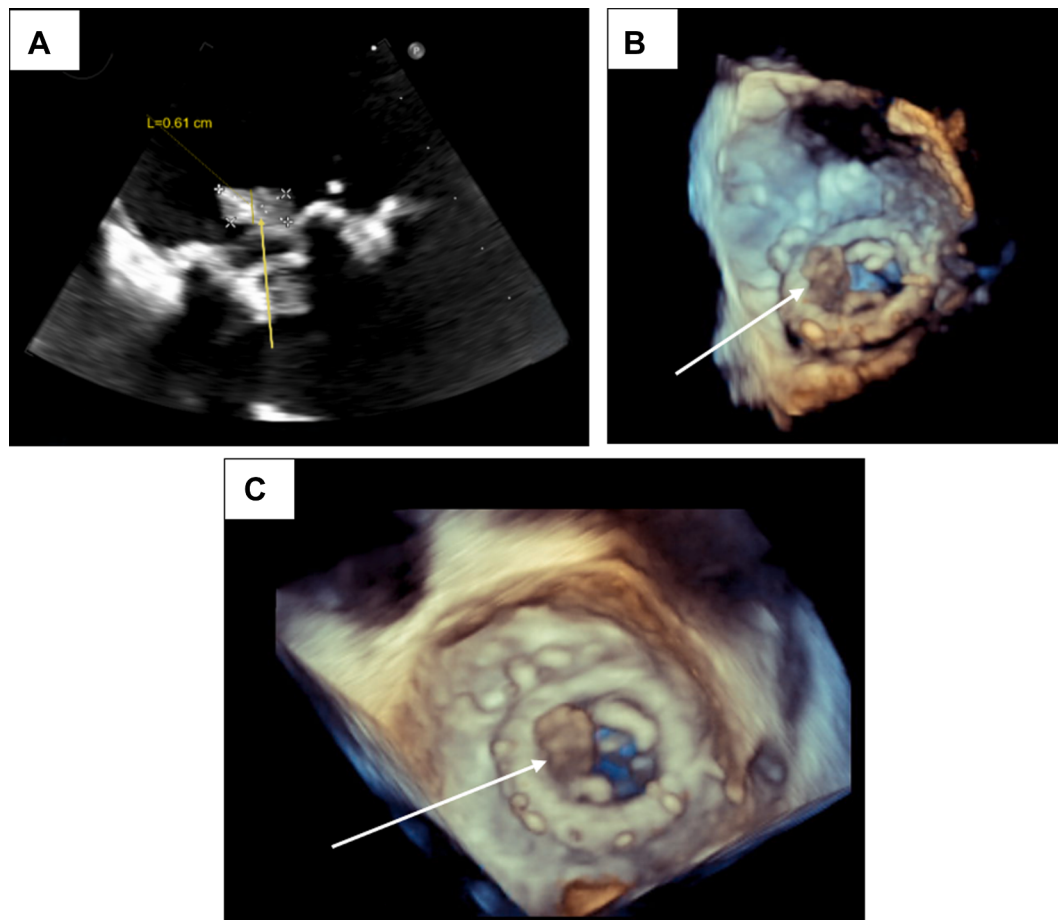
Over the following weeks, the patient gained weight and strength. Repeat transesophageal echocardiography on day 32 demonstrated stable vegetations. Owing to his frailty and multiple comorbidities, he was not deemed a surgical candidate and was managed medically with long-term antifungal therapy. He was discharged on day 43 with follow-up arranged with an ID physician, cardiologist, pulmonologist, and his primary care physician.

FOLLOW-UP

At his 4- and 12-week outpatient ID follow-up visits, the patient showed continued clinical improvement. Fungal blood cultures, repeated 4 weeks after initiation of antifungal therapy, were negative after extended incubation. Although pancytopenia persisted, it remained stable, and serum calcium levels were normal without specific intervention (Table 1). A repeat chest computed tomography scan at the 12-week post-discharge visit showed partial improvement of the right upper lobe mass and complete resolution of the left-sided pleural effusion (Figure 1). He remained adherent to lifelong isavuconazole therapy with good tolerance.

DISCUSSION

Histoplasmosis endocarditis is a rare form of fungal infective endocarditis, with only a limited number of

FIGURE 2 Vegetation Visualized on Bioprosthetic Mitral Valve

Transesophageal echocardiography showing a vegetation on the bioprosthetic mitral valve (yellow arrow in A; white arrows in B and C).

cases reported in the literature. It most commonly occurs in patients with underlying immunosuppression or prosthetic heart valves and typically manifests as culture-negative endocarditis.^{3,4} Confirmation of diagnosis frequently occurs postoperatively or post-mortem owing to the poor yield of fungal cultures. However, antigen detection in urine and/or serum often provides an early diagnostic clue.⁴

Although rare, reactivation of *Histoplasma* infection years, even up to 5 decades, after primary exposure is a recognized phenomenon, particularly in individuals with subtle or acquired impairments in immune function.^{5,6} Our patient lacked overt immunosuppression, but had classic risk factors for exposure (soil, rural setting, endemic area). His previous pneumonia episode may have represented an acute primary *Histoplasma* infection that seeded the prosthetic valve. We propose that multiple chronic comorbidities, including cirrhosis, type 2 diabetes,

advanced age, and recent diagnosis of untreated prostate cancer, likely contributed to waning immune surveillance and increased susceptibility to reactivation.

Diagnosis was challenging owing to negative cultures initially and nonspecific systemic findings. Beta-D-glucan, though nonspecific, and urinary antigen testing, a sensitive method for disseminated *Histoplasma*, were instrumental in diagnosis. Blood cultures for *H capsulatum* often require extended incubation and specialized media, highlighting the importance of early suspicion, use of noninvasive screening tests, and initiation of empirical antifungal therapy if the tests are positive.

Isavuconazole, an extended-spectrum triazole with improved tolerability and fewer drug interactions,^{1,2} was successfully used in this case. Although not first-line treatment per current guidelines,^{4,7,8} it offers a viable alternative for patients

TABLE 2 Infectious Diseases-Directed Laboratory Studies Showing Positive Screening Results for Histoplasmosis	
Laboratory Test	Results
Fungitell beta D-glucan	Positive
Histoplasma urine antigen	Positive
Lyme IgM (23 kDa)	Positive
Lyme IgG	All negative
Cryptococcus	
Aspergillus	
Coccidioides	
Bartonella	
Histoplasma	
Brucella	
Ehrlichia	
Legionella	
Leptospira	
Mycoplasma pneumoniae	
Q fever	
Spotted fever	
Bone marrow PAS staining	No microorganisms seen
Paraproteinemia studies	Negative
HIV screening	Negative
CD4 T-cells	428 (35.7%)
CD8 T-cells	492 (41%)

PAS = Periodic acid-Schiff.

with contraindications to itraconazole. Notably, our patient was managed without valve surgery, which is typically recommended in fungal PVE.^{4,7,9} This conservative approach may be suitable in select patients with stable hemodynamics, absence of large emboli, and robust clinical response to antifungals and who are not surgical candidates for various reasons.

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KEY WORDS echocardiography, endocarditis, mitral valve, valve replacement

APPENDIX For supplemental videos, please see the online version of this paper.

CONCLUSIONS

This case adds to the evolving understanding of *Histoplasma* PVE by emphasizing several key points: diagnostic confirmation through both urine antigen testing and fungal blood cultures, effective nonsurgical management in high-risk patients, and successful long-term treatment with isavuconazole. It also highlights the need to consider fungal pathogens in patients with prosthetic valves and relevant occupational or environmental exposures. Finally, it illustrates the importance of individualized antifungal therapy, especially when first-line agents are limited by contraindications.

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