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Case report

Graft versus *histoplasma* disease: A case of vascular graft infection

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ABSTRACT

Histoplasma vascular graft infection (VGI) is rarely reported, with only a handful of instances documented in the existing literature. Reporting *Histoplasma* VGI cases is important as they demonstrate previous treatment strategies and their outcomes. In this paper, we report a case of disseminated *histoplasmosis* with ascending aortic graft infection. Conservative therapy was attempted initially but failed, and our patient eventually required surgical graft explantation. Our case demonstrates the challenges in diagnosing and managing VGI caused by *Histoplasma capsulatum*.

Introduction

Vascular graft infection (VGI) is an uncommon but devastating complication of vascular reconstructive surgery [1,2]. Fungal pathogens are identified in only 2 % of VGI cases [3,4]. Among these fungal infections, *Histoplasma* has been documented in only a small number of instances [4–7]. The scarcity of literature describing *Histoplasma* VGI makes its diagnosis and management challenging. In this paper, we describe a case of ascending aortic graft infection with *Histoplasma capsulatum* treated successfully with antifungal therapy and graft explantation after failing an initial attempt of conservative medical therapy. Our case report contributes to the body of literature on *Histoplasma* VGI.

Case presentation

A 72-year-old man presented with a one-year history of recurrent fevers and unintentional weight loss. He had no localizing symptoms otherwise. His medical history was pertinent for prostate cancer, ascending aortic aneurysm repair with a Dacron graft 18 years ago, bicuspid aortic valve, chronic kidney disease, and hyperthyroidism. The patient was born and raised in Iowa and has not lived elsewhere. He had horses, dogs, and cats on his property. He had also cared for livestock before taking up a new job as a driver for a furniture store over the last 18 years.

Given his chronic febrile illness and prior cardiovascular history, the primary concern was an endovascular infection. The patient was admitted for workup. He had multiple negative bacterial blood cultures and a negative fungal/mycobacterial blood culture. A transesophageal echocardiogram showed a large echogenic luminal mass in the mid-ascending aorta with a sessile component (1.6 ×1.8 cm) and a small (1.0 ×0.2 cm) mobile component attached to it, raising concern for infected vegetation or a large atheroma with thrombus. No root abscess was identified. Subsequently, a cardiac computed-tomography (CT) scan showed a heterogenous, mobile, filling defect in the ascending thoracic aorta with calcifications attached to the anterior wall of the aortic graft, mostly resembling a chronic thrombus. A [18 F]Fluorodeoxyglucose Positron Emission Tomography and CT (FDG PET-CT) was obtained and showed increased activity along the ascending aorta (SUVmax 4.2) with new intraluminal linear increased density (Fig. 1a). There was also abnormally elevated splenic activity (SUVmax 5.7) with borderline splenomegaly and mild diffuse bone marrow activity. No FDG avid lymphadenopathy was detected. At that point, the constellation of radiographic findings was thought to represent a thrombus rather than an infected vegetation. The patient was started on anticoagulation therapy.

Further workup was done to understand the cause of his febrile illness. A bone marrow biopsy showed normocellular marrow with trilineage hematopoiesis and two small non-necrotizing granulomata with negative Grocott's methenamine silver (GMS) staining. The patient also had cerebrospinal fluid (CSF) analysis due to a brief episode of confusion, with an unremarkable profile including clear fluid, normal opening pressure, and only two nucleated cells/μL. A panel of serological studies was also tested (see Table 1). His urine was positive for Blastomyces antigen (Ag) (5.4 ng/mL) and *Histoplasma* Ag (below the level of quantification; <0.2 ng/mL). His serum *Histoplasma* Ag was 3.1 ng/mL.

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He also had a positive *Histoplasma* M band on CSF. Ultimately, the serum *Histoplasma* complement fixation (CF) showed significantly elevated titers for both the Mycelial (1:1024) and Yeast (1:256) forms. Moreover, his serum *Histoplasma* immunodiffusion was positive for both the M and H bands. *H. capsulatum* DNA was also detected in blood on cell-free next-generation sequencing (Karius Test®). All remaining serum serologies were unremarkable.

Considering these new findings, the patient was diagnosed with disseminated *histoplasmosis* and the vascular graft mass was considered infected. As such, he was started on intravenous (IV) liposomal amphotericin B (AMB) 3 mg/kg once daily. He developed severe back pain with liposomal AMB infusions and was switched to IV lipid complex AMB at 5 mg/kg daily, which he tolerated. Cardiovascular surgery deemed the patient a poor candidate for graft explantation and replacement due to comorbidities and suggested conservative medical management. He was discharged to finish two weeks of AMB, followed by lifelong itraconazole therapy (200 mg twice daily). Itraconazole was started while on AMB to allow time to achieve therapeutic levels. After two weeks, the serum drug level for itraconazole was 1.2 μg/mL and hydroxyitraconazole 2.1 μg/mL, which was at goal (goal itraconazole level $\geq$1.0 μg/mL). Hence, AMB was stopped, and the patient continued itraconazole alone.

The patient progressed poorly during medical management. He developed worsening fatigue and had episodes of anemia requiring transfusions. His *Histoplasma* and Blastomyces urine Ag increased to 1.4 ng/mL and 17.3 ng/mL, respectively. He was admitted again a few months following the initial presentation with septic emboli to bilateral lower extremities as well as to the brain. Magnetic resonance imaging (MRI) showed several nodular foci of enhancement throughout the brain. A repeat PET-CT showed progression of FDG avidity in the ascending aortic graft along with infectious emboli in the lower extremities (Fig. 1b). He was started again on liposomal AMB and, this time, tolerated it; itraconazole was held. With this progression, the patient underwent redo sternotomy, explantation of the infected graft, and in-situ Bentall root replacement with tissue aortic valve and reconstruction of the aortic arch using a new Dacron graft. The surgery was done almost three months after his initial presentation. A huge "fungal ball" was found attached to the proximal suture line of the excised graft and covering the orifice of the aorta. Histopathology showed an infected thrombus with organisms morphologically consistent with *Histoplasma*. Fungal smear on excised tissue showed yeast and pseudohyphae, but both *Histoplasma* polymerase chain reaction (PCR) and fungal cultures were negative.

His postoperative course was complicated by acute kidney injury requiring dialysis for one month and atrial fibrillation requiring amiodarone initiation, which prolonged his QTc. He required permanent pacemaker placement. His liposomal AMB infusions were spaced out to three times weekly. Due to prolonged QTc, the patient remained on AMB for 8 weeks after surgery until isavuconazole finally became available. He was switched to isavuconazole 372 mg daily for life-long suppression with a serum drug level target of $>$ 1.0 μg/mL. He had a transthoracic echocardiogram done two months following surgical intervention for VGI, which showed normal structure of the new tissue arotic valve and aortic graft. His urine and serum *Histoplasma* Ag became undetected after two and three months from surgery, respectively (Table 1). He continues to follow up with infectious diseases, cardiovascular surgery, and nephrology. He is tolerating therapy with isavuconazole and is symptom-free. Given his reassuring clinical and serological follow-up, a

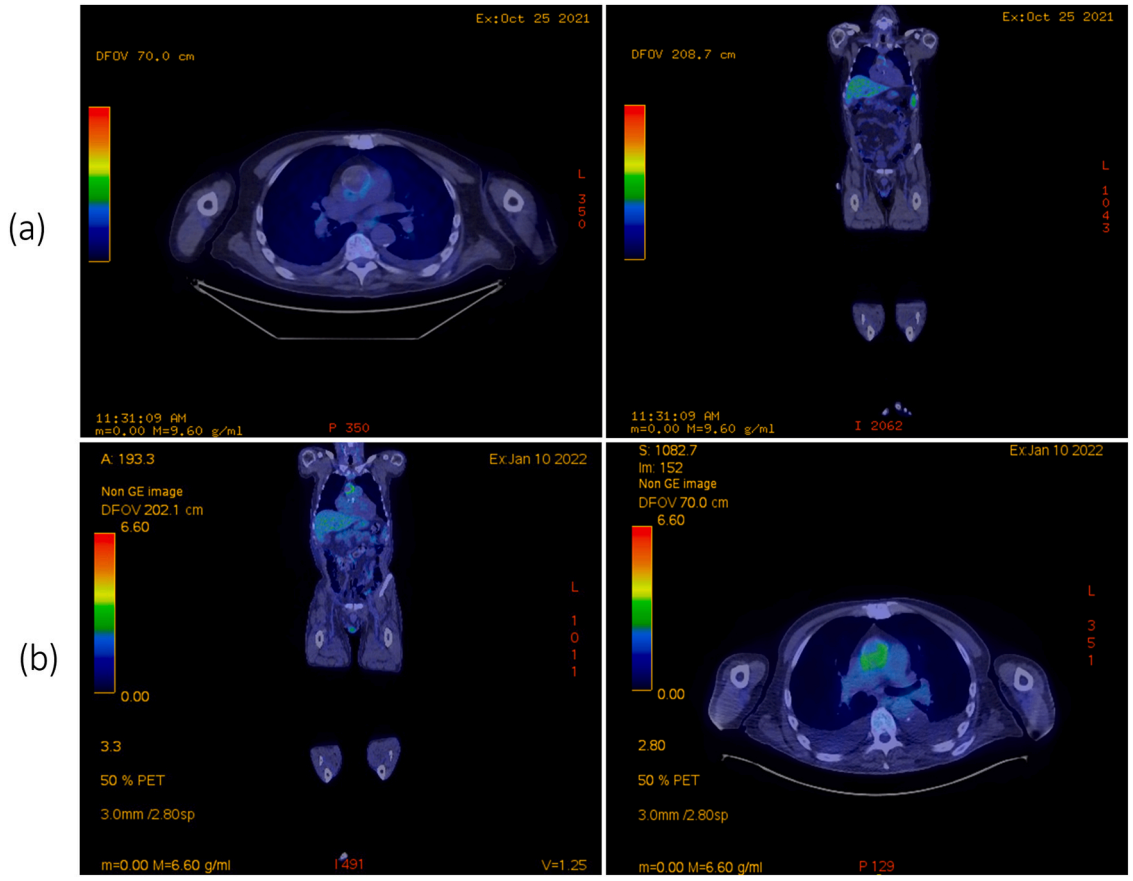

Fig. 1. (a) [18 F]Fluorodeoxyglucose Positron Emission Tomography and CT (FGD PET-CT) obtained on initial presentation showed intraluminal linear high density at the superior margin of the ascending aorta graft with partially circumferential FDG uptake along the intraluminal density and about the aorta extending to the aortic root. (b) Repeat PET-CT on readmission showing interval progression of FDG avid mycotic infection involving the root of the aorta.

Table 1
outlines the serological workup.

	Reference	Presentation	Readmission	1 month post-surgery
Anaplasma phagocytophilum IgG, serum	< 1:64	< 1:64	-	-
Ehrlichia Chaffeensis IgG, serum	< 1:64	< 1:64	-	-
Babesia microti IgG, serum	< 1:64	< 1:64	-	-
HIV 1-/2- Antigen and Antibody screen, plasma	Negative	Negative	-	-
Syphilis total Antibodies with reflex to RPR	Nonreactive	Nonreactive	-	-
Hepatitis C total Antibodies, serum	Negative	Negative	-	-
Hepatitis B surface Antigen, serum	Negative	Negative	-	-
Bartonella PCR, blood	Negative	Negative	-	-
Brucella IgM and IgG ELISA, serum	Negative	Negative	-	-
Q-fever IgM and IgG, blood	< 1:16 (for all phases)	< 1:16 (for all phases)	-	-
Tropheryma whipplei PCR, blood	Negative	Negative	-	-
Coccidiodes antibody screen, serum	Negative	Negative	-	-
Blastomyces Ab, immunodiffusion	Negative	Negative	-	-
Histoplasma complement fixation, (Mycelial)	Negative	**1:1024**	-	**1:64**
Histoplasma complement fixation, (Yeast)	Negative	**1:256**	-	**1:128**
Histoplasma immunodiffusion	H(-) and M (-)	H(+) and M (+)	-	H(+) and M (+)
Histoplasma Ag, Quantitative EIA, Urine	Not detected	**< 0.2**	**1.4**	**0.4**[a]
Blastomyces Ag, Quantitative EIA, Urine	Not detected	**5.4**	**17.3**	**< 1.3**
Histoplasma Ag, Quantitative, Serum	Not detected	**3.1**	**1.4**	**1.0**[b]

[a] Became undetected after 2 months from surgery.
[b] Became undetected after 3 months from surgery.

repeat CT or PET-CT was not performed. His last follow-up at the time of this writing was twenty-two months after graft explantation.

Discussion

Our report highlights the difficulties in diagnosing and treating *Histoplasma* VGI. In our patient, the diagnosis of *Histoplasma* was made through serum serology, serum and urine Ag, and tissue histopathology, while fungal cultures of blood and aortic tissue and tissue *Histoplasma* PCR all remained negative. The initial reliance on medical therapy alone led to a complicated course with peripheral septic emboli and our patient eventually required surgical explantation of infected graft and vascular reconstruction. This underscores the importance of source control through surgical explantation of infected graft in fungal VGI.

Histoplasma has been rarely reported in cases of cardiovascular infections, such as native and prosthetic valve endocarditis (IE), endarteritis, aortitis, and VGI [6,7]. Nonetheless, it should always be considered on the differential for any culture-negative VGI in patients with epidemiologic risk factors such as history of residence in an endemic area or high-risk activities like spelunking or excavation [7]. Our patient resided in an endemic area, which prompted an investigation for *histoplasmosis*.

Table 2 lists a handful of *Histoplasma* VGI cases documented in the literature [4–7]. Several key points can be drawn from these cases. While disseminated *histoplasmosis* primarily affects immunocompromised hosts, all reported patients were immunocompetent which indicates that *Histoplasma* can occur with normal host immunity. Notably, it can present many years after index arterial reconstructive surgery and often in the form of chronic febrile illness with no localizing signs or symptoms specific for graft infection. Interestingly, none of the prior cases reported evidence of pulmonary infection. This was also the case in our patient who had no pulmonary lesions on radiography. Without a high index of suspicion, *Histoplasma* VGI can be easily missed. But even when suspected, confirming the presence of VGI is quite challenging due to the lack of conclusive noninvasive diagnostic tests. Radiography, including nuclear medicine scans, plays a pivotal role in gauging suspicion for VGI, which can then drive decision for graft explantation and direct examination of infected tissue. Importantly, signs of infection may be absent on initial radiographic scans but may appear on repeat imaging when there is continued concern for VGI [6].

Furthermore, proving the involvement of *Histoplasma* with the infected graft is a difficult task due to the fastidious nature of this pathogen. A significant delay from time of presentation for VGI to microbiologic diagnosis of *Histoplasma* was evident in all prior reports [4,6,7]. Similar to our case, the initial evaluation is often based on serum serologies and serum/urine Ag which are often detected in case of disseminated *histoplasmosis*. In a prior series including five patients with endovascular *histoplasmosis* (three with IE, two with VGI) [7], all patients had positive serum serologies with a median peak mycelial CF titer of 1:1024 and a median peak yeast CF titer of 1:512. Additionally, all patients from this series had positive serum immunodiffusion, with four patients having both H and M bands and one patient having H band alone [7]. Furthermore, while our patient's blood cultures remained negative, some prior cases had positive growth of *H. capsulatum* on blood cultures albeit delayed as expected [6]. Notably, our patient had detectable DNA for *H. capsulatum* in blood using a blood microbial cell-free DNA next generation sequencing test (Karius®). This diagnostic modality has recently been gaining attention in cardiovascular infections such as IE [8]. At best, the aforementioned indirect tests can be supportive of the diagnosis of *Histoplasma* VGI but ultimately the only definitive means for confirming the diagnosis is through histopathologic and microbiologic evaluation of graft or perigraft specimen obtained percutaneously or during surgical explantation [9,10].

When radiography and ancillary tests are supportive of VGI, the optimal management includes complete graft explantation with vascular reconstruction followed by antimicrobial therapy [9,11]. This may be particularly important with fungal VGI due to risk of embolization. Embolic events with *H. capsulatum* cardiovascular infections are commonly reported in published cases [5,7]. However, the benefit of early graft explantation on preventing systemic embolization with *Histoplasma* VGI can only be hypothesized but not confirmed due to scarcity of data on this topic. Nonetheless, many patients with VGI are not fit for surgery and may be offered conservative suppressive management at first, which consists of graft preservation with antimicrobial therapy. There is only one case in the literature whereby medical therapy was successfully used alone for the treatment of a *Histoplasma* VGI [6]. The patient was alive 18 months after the diagnosis, with pseudoaneurysm resolution. Therefore, ours is the second documented case attempting medical therapy alone for the management of *Histoplasma* VGI but our experience led to a complicated course as opposed to the prior report.

When the graft is explanted, a fungal ball seen on gross inspection of the graft can provide clue to a fungal etiology. Furthermore,

Table 2
Summary of *histoplasma* VGI cases documented in the literature.

[Ref] Age, y/ Sex	Graft location	Time from implant to presentation, y	IC	Time from presentation to diagnosis, mo	Presentation	*Histoplasma* tests	Radiographic evaluation	Medical management	Surgical management	Tissue examination diagnostic of *Histoplasma*	**Outcome**
[7] 31/M	AR/AA	11	No	4	Chronic fevers.	• Mycelial CF: 1:512 • Yeast CF: 1:512 • ID: M + H • Urine Ag: positive • Serum Ag: NR	• Cardiac MRI: linear density within graft. • TEE: mobile echodensity within graft.	AMB followed by lifelong itraconazole.	Graft excision and replacement with distal homograft implant.	Yes	Alive at 7 months.
[7] 56/M	AA	2	No	6	Chronic fevers.	• Mycelial CF: 1:512 • Yeast CF: 1:64 • ID: NR • Urine Ag: positive • Serum Ag: NR	NR	AMB followed by lifelong itraconazole.	Graft excision and replacement (details not provided).	Yes	Alive at 10 years.
[4] 68/M	AFB	NR	No	0.5	Ischemic rest pain. Was undergoing a second bypass procedure. The procedure was aborted due to "incidental" intraoperative findings suggestive of infection.	NR	• WBC-scan: normal. • CT: pseudoaneurysm and subtle rim of edema around graft.	Oral itraconazole (3 months)	Graft excision and replacement with neoaortoiliac system.	Yes	Good clinical recovery but follow-up duration not specified.
[6] 68/M	AFB	13	No	7	Unintentional weight loss, night sweats, dry cough, and generalized fatigue. Pulsatile mass on exam over right femoral area.	• Serology: negative[a] • Serum Ag: UD • Urine Ag: UD • Blood cultures: *H. capsulatum*	• CXR: normal. • PET-CT: splenomegaly with mild diffuse splenic uptake. • US: common femoral artery aneurysm with hematoma. • WBC-scan: increased uptake at the graft.[b]	AMB followed by lifelong itraconazole.	None	None	Alive at 18 months.
[5] 55/M	AFB	10	No	120	Weight loss, anorexia, and lethargy. Left leg claudication and rest pain. History of disseminated *histoplasmosis* diagnosed and treated 10 years previously after biopsy of a tongue ulcer.	NR	• Aortography: false aneurysm at the anastomotic site.	Ketoconazole for one year[c].	Graft excision and replacement with a Dacron aortobifemoral graft.	Yes	Alive at 26 months.

Abbreviations: AA: ascending aorta; AFB: aortofemoral bypass; AR: aortic root; IC: immunocompromised; NR: Not reported; UD: undetected.
[a] labeled as "fungal" serology.
[b] Initial WBC-scan was negative.
[c] Case dates back to 1979

demonstration of yeast on histopathology or isolation of the mold on cultures from graft or perigraft tissue is the gold standard for diagnosing *Histoplasma* infection as previously outlined [10,12]. Since the pathogen may be difficult to grow on cultures, histopathology plays an essential role in this setting. This was seen in our case where histopathology showed forms consistent with *Histoplasma* but cultures remained negative. Similarly, all reported patients with *Histoplasma* VGI treated with graft excision had yeast or hyphae forms consistent with *Histoplasma* on histopathology [5–7].

In individuals with disseminated *histoplasmosis*, liposomal AMB is the drug of choice, followed by maintenance treatment with itraconazole [4,6,7,13]. In contrast, our patient was put on maintenance therapy with isavuconazole instead of itraconazole due to QTc prolongation. As such, our case is the first to demonstrate good clinical recovery with isavuconazole for *Histoplasma* VGI, with an approximate two-year follow-up period. The optimal duration for antifungal therapy for *Histoplasma* VGI is unknown but lifelong maintenance antifungal therapy is reasonable due to concerns of relapse, similar to our case. In a previous case, authors reported good clinical recovery with a 3-month itraconazole course following neoaortoiliac system reconstruction but the follow-up duration was not specified [4]. Patients managed for *Histoplasma* VGI should be monitored closely for treatment response. This includes serial monitoring of serum and urine Ag [13], and routine clinic follow-up.

Conclusion

Our case highlights the need to consider atypical organisms such as *H. capsulatum* when it comes to VGI, particularly when specific epidemiological conditions are present and conventional infectious workup is unrevealing. Additionally, it underscores the significance of surgical intervention, especially when conservative treatment proves insufficient.

Ethical approval

This work did not require ethical approval.

Funding source

None.

Consent

Consent to publish was not obtained since the case report does not contain any personal identifiers. However, the patient did provide permission for the use of his medical record for research through the Minnesota Research Authorization process.

Prior presentations/publications

None.

Author statement

We certify that all authors have participated in the conception and design of this work, as well as the writing of the manuscript, to take full public responsibility for it. All authors have seen and approved the manuscript, contributed significantly to the work. A conflict-of-interest statement is included in the manuscript. The manuscript has neither been previously published nor is being considered for publication elsewhere.

CRediT authorship contribution statement

Racha Ghoussaini: Writing – review & editing, Writing – original draft, Visualization. **Omar Abu Saleh:** Writing – review & editing, Supervision, Conceptualization. **Hussam Tabaja:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Conceptualization.

Conflict of interest

All authors involved in this work declare no conflict of interests.

Data Availability

The data used to write this case report is not accessible to public.

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