Rare case of *Histoplasma capsulatum* endocarditis in a patient with a prosthetic valve

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**Background**
Diagnosis of fungal endocarditis can be challenging, especially among cases with negative blood culture results. Of fungal endocarditis cases, *Histoplasma capsulatum* constitutes an even smaller proportion with \( \leq 58 \) prior cases reported. Due to the rarity of histoplasmosis endocarditis and thus limited data, there is no current diagnostic guideline for testing within culture negative infective endocarditis.

**Case summary**
Our patient was a 58-year-old female presenting with worsening dyspnoea, hypotension, and near-syncope. In this case report, we depict the clinical presentation and diagnosis of *H. capsulatum* endocarditis in a female patient with a prosthetic aortic valve and negative blood cultures. We further demonstrate the rising risk of fungal endocarditis with use of external devices.

**Discussion**
Despite the rarity of fungal endocarditis, there has been a recent upward trend in infections given the rising use of external devices, greater number of immunocompromised patients, and rising rates of intravenous drug use. Recently, more cases of fungal endocarditis have been occurring in patients with prosthetic valves compared to native. Although *H. capsulatum* constitutes a smaller proportion of fungal endocarditis cases, patients with appropriate risk factors and those who have been exposed to at-risk areas such as the Ohio and Mississippi River valleys, may benefit from further evaluation.

**ESC Curriculum**
4.10 Prosthetic valves • 4.11 Endocarditis

**Learning points**
- Educate about rising risk of fungal endocarditis in patients with external devices and guide approach of culture negative infective endocarditis.
- To recognize *Histoplasma capsulatum* as a potential cause of infective endocarditis.

**Introduction**
Fungal endocarditis is rare with a mortality rate of \( \approx 50\% \). Among fungal endocarditis cases, infections caused by *H. capsulatum* comprise an even smaller subset. Furthermore, Histoplasma endocarditis remains difficult to diagnose, often presenting with negative cultures and necessitating an underlying level of suspicion for further testing methods. Such tests may take days before providing results, creating further challenges and delays. Given the rising risk of fungal endocarditis and its high mortality rate, effective diagnosis is crucial. This case...
report describes the clinical presentation and diagnosis of *H. capsulatum* endocarditis in a female patient with past medical history of a prosthetic aortic valve.

**Timeline**

| Time                   | Events                                                                 |
|------------------------|------------------------------------------------------------------------|
| Aortic valve and root replacement, 9 years prior | Patient received a Carpentier-Edwards Magna Ease pericardial aortic bioprosthesis #21 and aortic root replacement for bicuspid aortic valve stenosis with ascending aortic aneurysm. |
| Patient presents to local cardiologist with shortness of breath, in April | Patient started on apixaban due to concern for valve thrombosis from transoesophageal echocardiogram. |
| Re-presents to local cardiologist with hospital admission on 22 May | New hypotension and near-syncope, with worsening dyspnoea patient was admitted to her local hospital. |
| Transfer and admission to our coronary intensive care unit on 23 May | Initial negative blood cultures. Imaging and further labs revealed *Histoplasma capsulatum* endocarditis. Infectious disease and cardiothoracic surgery were consulted. |
| Management for haemodynamic instability, from 23 May to 31 May | Patient received blood product transfusions, vasopressors and an intra-aortic balloon pump. |
| Transitioned to comfort care on 31 May | Despite treatment, patient’s health progressively declined, and she passed away. |

**Case presentation**

A 58-year-old Caucasian female was admitted to our coronary intensive care unit due to progressive dyspnoea and haemodynamic instability. The patient’s past medical history included a bicuspid aortic valve complicated by stenosis and an ascending aortic aneurysm status post-successful aortic valve replacement (Carpentier-Edwards Magna Ease pericardial aortic bioprosthesis #21) and aortic root replacement performed 9 years prior. Past medical history was also significant for sarcoidosis with stage II lung disease and neurosarcoidosis which remained stable for many years on methotrexate and leucovorin at the time of admission. One month prior to admission, she experienced shortness of breath, and presented to her local cardiologist who performed a transoesophageal echocardiogram (TOE). Due to concern for thrombosis of her bioprosthetic aortic valve, she was started on 5 mg b.i.d. apixaban. She developed worsening dyspnoea, hypotension, and near-syncpe and was thus admitted. Vital signs included a blood pressure of 102/46, heart rate of 97 beats per minute, respiratory rate of 30 breaths per minute, \(\text{SpO}_2\) of 93%, and a temperature of 36.3°C. Physical examination revealed elevated jugular vein distention, harsh III/VI systolic ejection murmur with loss of S2, bilateral pulmonary rales, and cold lower extremities.

After admission to the coronary intensive care unit, a chest X-ray was performed and revealed bilateral diffuse reticular opacities (Figure 1).

Both a transthoracic echocardiogram (TTE) and TOE were performed. Transthoracic echocardiogram revealed a reduced left ventricular ejection fraction of 49% and severe aortic valve stenosis due to prosthetic thickening and calcification. The peak gradient was 109 mmHg (peak velocity = 521.7 cm/s) with a mean gradient of 73 mmHg (Figure 2) (mean velocity = 353.7 cm/s). The dimensionless valve index was 0.17. In addition, there was moderate mitral regurgitation with normal right ventricular function, trace tricuspid regurgitation, and a dilated and non-collapsible inferior vena cava.

Transoesophageal echocardiogram supported the finding of severe aortic valve stenosis with marked thickening of the cusps (Video 1). Additionally, there was evidence of paravalvular leak with suggestion of partial dehiscence of the bioprosthesis and perivalvular abscess, highly raising suspicion for an infectious process. Her atriointimal conduction remained intact with a PR interval of 170 ms (Video 2).

The patient’s blood work revealed: N-terminal-pro hormone B-type natriuretic peptide (NT-proBNP) of 58 534 pg/mL (normal: <300 pg/mL), C-reactive protein of 4.3 mg/L (normal: <0.8 mg/dL), erythrocyte sedimentation rate of 5 mm/h (normal: 0–20 mm/h), plasma: platelet factor 4 complex of 0.222 (negative: <0.4), lactate of 1.1 mmol/L (normal: 0.7–2.1 mmol/L), and pancytopenia [haemoglobin 10.1 g/dL (normal: 12–16 g/dL) with a reticulocyte index of 0.25 (normal: 0.5–1.5), platelet count 65 000/μL (normal: 150 000–450 000/μL), white blood cell count 5700/μL (normal: 4000–11 000/μL)]. Her labs indicated disseminated intravascular coagulation including a d-Dimer of 1840 ng/mL (normal: <500 ng/mL) and fibrinogen of 108 mg/dL (normal: 200–400 mg/dL). Her peripheral smear was unrevealing. Blood cultures were negative for growth. Further
investigations revealed 1,3-b-d-glucan >500 pg/mL (normal: <60 pg/mL), Histoplasma urine antigen 17.5 ng/mL (normal: negative result), and Histoplasma antibody positive, confirming diagnosis of H. capsulatum endocarditis.

Due to concerns for her haemodynamic instability, the patient was supported via blood product transfusions (>10 units of blood products) and norepinephrine at 10 mcg/kg/min. Despite this, she developed worsening hypotension, and an intra-aortic balloon pump was placed to maintain a mean arterial pressure above 60 mmHg. Surgical consultation was requested however, due to the patient’s critical illness, she was deemed not a candidate for surgical aortic valve replacement. Infectious disease was consulted for consideration of empiric antifungal therapy, in which they recommended vancomycin, ceftriaxone, and liposomal amphotericin B. However, the patient’s condition deteriorated, and she was transitioned to comfort care. The patient succumbed to her disease and passed away.

On autopsy, gross examination revealed bulky occlusive vegetations of the bioprosthetic aortic valve and ascending aortic graft. Histopathological examination demonstrated disseminated
Histoplasmosis involving the heart, lungs, kidneys, adrenal glands, mediastinal lymph nodes, brain, and spinal cord (Figure 3).

Discussion

Fungal endocarditis is a rare albeit fatal disease, accounting for 1% of all cases of endocarditis and 4% of prosthetic valve endocarditis with a mortality rate of ~50%. Risk has been increasing, given the rising use of external devices such as implantable cardioverter-defibrillator/pacemakers and prosthetic heart valves, greater number of immuno-compromised patients, and rising rates of intravenous drug use. In recent years, prosthetic valves have constituted more cases of fungal endocarditis than native valves. Primarily, fungal endocarditis infections are most commonly caused by Candida and Aspergillus species. Of fungal endocarditis cases, *H. capsulatum* constitutes a smaller proportion of cases. Although the overall incidence of dimorphic fungal endocarditis (such as *H. capsulatum*) remains low, consideration should be made for those who have been exposed to endemic regions. *Histoplasma capsulatum* is endemic to the Ohio and Mississippi River valleys, but rarely manifests as endocarditis with ~58 prior cases reported. Other common dimorphic fungi that should be considered include: Blastomyces dermatitidis (endemic to Ohio and Mississippi River valleys, the Great Lakes, and the Saint Lawrence River), Coccidioides immitis (endemic to southwest USA, Mexico, and South America), and Paracoccidioides brasiliensis (endemic to Central and South America). While these dimorphic fungi rarely cause endocarditis, residence or travel to affected regions should be obtained during initial patient history to ensure proper and timely diagnosis. Our patient had the risk factors of both a prosthetic valve and residence within a *H. capsulatum* endemic region; these combined with our clinical suspicions of endocarditis—despite negative blood cultures—led us to further investigate a fungal cause.

Challenges and delays in diagnosis of Histoplasma endocarditis remain considerable as 80% of blood cultures present negative. Beta-d-glucan and galactomannan are more sensitive and specific but require an underlying level of suspicion and often take days before the test results.

Furthermore, there is no current diagnostic guideline for testing for Histoplasma within culture negative infective endocarditis. As such, diagnostic testing of *H. capsulatum* endocarditis has shifted to antigen detection within the urine and serum, with an approximate sensitivity of 90% for disseminated disease. Additionally, imaging plays a vital role. Echocardiograms allow for visualization of clinical complications such as vegetations and dehiscence as seen in our case. The first line imaging technique with suspicion of infective endocarditis is TTE. If the patient is at high initial risk (ex: prosthetic heart valves, heart failure, etc.), or if TTE is positive or non-diagnostic, a TOE is also recommended. Furthermore, prior studies have shown that TOE has a high sensitivity and specificity for prosthetic valve endocarditis—and compared to other methods—may be superior in identifying prosthesis dehiscence, paravalvular leaks, and vegetations (Figure 3).
other complications.\textsuperscript{9} Other diagnostic imaging techniques shown to be useful include multislice computed tomography and \textsuperscript{18}F-fluorodeoxyglucose positron emission tomography.\textsuperscript{9,10}

Fungal endocarditis often mimics bacterial endocarditis. The most common presentation in fungal endocarditis is fever.\textsuperscript{1,4} Other common clinical features may include dyspnoea, presence of a new murmur, weakness, tachycardia, valve regurgitation, heart failure, and pleuritic chest pain.\textsuperscript{1} This aligns with many of the physical examination findings in our patient.

Due to the rarity of histoplasmosis endocarditis and the lack of data surrounding treatment, there are limited evidence-based guidelines. Nevertheless, the literature has suggested two primary treatment steps including surgical replacement of the valve (if possible) and the fungicidal agent—amphotericin B.\textsuperscript{3,4,6} Antifungal therapy generally lasts for greater than 6 weeks.\textsuperscript{3} Afterwards, lifelong suppression via an oral azole (most often itraconazole) is reasonable to prevent relapse or for those deemed to be poor surgical candidates.\textsuperscript{3,4} Furthermore, for replacement of prosthetic valves in fungal endocarditis, as seen in our patient, homografts have been favoured over prostheses.\textsuperscript{2}

Conclusions

\textit{Histoplasma capsulatum} endocarditis is an uncommon form of endocarditis with a high mortality rate. In this case report, we describe the clinical presentation and management of \textit{H. capsulatum} endocarditis, a rare complication of the fungal infection. Our case report and prior literature suggest that culture negative infective endocarditis should include workup of potential fungal causes, especially for patients with appropriate risk factors and those who have been exposed to at-risk areas.

Lead author biography

Emily M. Manning is a medical student at Case Western Reserve University School of Medicine. She graduated with a Masters in Physiology from North Carolina State University and a Bachelor’s in Public Policy with a concentration in U.S. and Global Health from the University of North Carolina at Chapel Hill.

Supplementary material

Supplementary material is available at European Heart Journal - Case Reports online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

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