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Case report

Aspergillosis myocarditis in the immunocompromised host

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ABSTRACT

Invasive cardiac aspergillosis has been rarely described in immunocompromised patients. This disease is difficult to diagnose by conventional laboratory, microbiologic, and imaging techniques, and is often recognized only post-mortem. The authors present the case of a 60-year-old woman admitted with an exacerbation of eosinophilic granulomatosis with polyangitiis (EGPA) who subsequently died from *Aspergillus* myocarditis, and compare the patient's case to prior literature. This serves as an up-to-date literature review on the topic of invasive cardiac aspergillosis.

Introduction

Invasive aspergillosis from one of several species of *Aspergillus* fungi is a well-described, common, and morbid disease in immunocompromised hosts [1]. Infective endocarditis from aspergillosis has also been extensively described, and is second only to Candida species as a fungal etiology of infective endocarditis [2]. However, myocarditis from aspergillosis, describing aspergillus invading into the parenchyma of the heart, has been very rarely described, and remains a notably uncommon manifestation of angioinasive aspergillosis [3–5].

What limited prior literature exists on aspergillosis myocarditis suggests that the host is invariable significantly immunocompromised and that outcomes are poor. Risk factors have included solid-organ and hematopoietic stem cell transplantation, chemotherapy, high-dose glucocorticoids, and human immunodeficiency virus (HIV) infection patients with acquired immunodeficiency syndrome (AIDS) [6–8]. In prior reports, the presentation of aspergillosis myocarditis is variable, including cardiac tamponade[5], myocardial infarction [9–12], and complete heart block [12]. The clinical course is often fulminant and mortality exceeds 90%(8) and there are often concomitant widespread metastatic foci of infection. In the majority of published cases, the diagnosis of cardiac-invasive aspergillosis was not made until postmortem autopsy examination. Here, we describe the case of a patient who died as a result of aspergillosis myocarditis, and review prior literature on this morbid fungal infection.

Case report

A 60-year-old woman with eosinophilic granulomatosis with polyangiitis (EGPA; formerly known as Churg-Strauss syndrome) and idiopathic dilated cardiomyopathy presented with three weeks history of progressive exertional dyspnea and bilateral lower extremity swelling. Two years prior, in work-up for her dilated cardiomyopathy, a left heart catheterization revealed normal coronary arteries and cardiac magnetic resonance imaging and myocardial biopsy revealed no specific etiology. Medications on admission were notable for albuterol, fluticasone-salmeterol, metoprolol succinate, spironolactone, and torsemide. Her social history was notable for previous employment as an artist making mobiles, minimal alcohol use, and no history of tobacco or recreational drug use. Family history was remarkable for a father who died of colon cancer.

On initial presentation, vital signs were temperature 36.8 °C, blood pressure 93/55 mmHg, pulse 114 beats per minute, respiratory rate 16 breaths per minute, and oxygen saturation 100% on room air. Physical examination revealed tachycardia with normal heart sounds without appreciable murmur, normal work of breathing with clear lung fields, and 1+ bilateral lower extremity edema. Laboratory testing revealed white blood cell count of 7×10^3 cells/μL with a differential of 64% neutrophils, 18% lymphocytes, 11% monocytes, and 6% eosinophils. Hemoglobin was 12.8 g/dL, and platelet count was 262×10^3/ μL. Chest X-ray revealed cephalization of pulmonary vasculature, suggestive of hydrostatic pulmonary edema. Transthoracic echocardiography

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revealed a left ventricular ejection fraction (LVEF) of 15%, significantly reduced from one year prior (LVEF of 35%), without valvular vegetations or intracardiac abscesses. She was treated with diuretics and methylprednisolone 250 mg every six hours for suspected EGPA flare, with plan for repeat cardiac MRI. However, on hospital day three, she suffered an acute respiratory decompensation requiring endotracheal intubation. Chest X-ray revealed new left upper lobe infiltrates and bilateral pleural effusions, and she was started on ceftriaxone 1 g intravenous daily and azithromycin 500 mg orally daily for presumed community-acquired pneumonia. Bronchoscopy with alveolar lavage (BAL) showed no evidence of diffuse alveolar hemorrhage and no overt evidence of infection. Infectious work-up including (1–3)-beta-d-glucan, urine antigens for *Streptococcus pneumoniae* and Legionella, and blood and sputum cultures, was unrevealing. Given ongoing concern for EGPA flair, she was given rituximab 540 mg and corticosteroids were increased to methylprednisolone 1000 mg daily. She rapidly developed anuric renal failure and cardiogenic shock requiring inotropic support. Her condition continued to deteriorate and in consultation with her family, the decision was made to transition to a comfort-directed plan of care and she expired. The family requested autopsy, which revealed invasive myocarditis secondary to *Aspergillus fumigatus* as well as multiple myocardial abscesses (Fig. 1).

Discussion

We present the case of an unfortunate immunocompromised 60-year-old woman with EGPA who died of aspergillus myocarditis and pneumonia that was not diagnosed until after her death. Unfortunately, as this case demonstrates, afulminant fatal course and missed diagnosis pre-mortem is emblematic of the disease. We reviewed PubMed and identified 39 prior cases of aspergillus myocarditis. Results of literature review are shown in Table 1.

The majority of published cases of aspergillus myocarditis affected men and the median age was 41 (range 16–81) years old. Risk factors include chemotherapy, immunosuppressive therapy, glucocorticoids, and poorly-controlled AIDS - the latter of which was historically not considered a common association for invasive aspergillosis [15], but represented a significant percentage (28%) in this series. While widespread concomitant sites of infection were commonly observed, most had no pre-mortem suggestive cardiac imaging findings and only 18% were diagnosed pre-mortem. *Aspergillus* is rarely isolated from premortem blood cultures [8], which was observed in the Xie et al. series in which only 12% of cases had positive blood cultures. *Aspergillus fumigatus* was the most commonly observed species (44%), followed by *A. flavus* (38%), and *A. terreus* (5%). A fatal course was observed in 95% of cases.

Definitive diagnosis of disseminated aspergillosis requires culture from a normally sterile site with histopathologic evidence of tissue invasion. The galactomannan enzyme immunoassay (GM) tests for a polysaccharide component of the cell wall of *Aspergillus* spp. and can be used on both serum and BAL specimens as a diagnostic aid. The sensitivity and specificity of serum GM are 82% and 81%, respectively, and a galactomannan test is most useful in patients with hematologic malignancies or those who have undergone hematopoietic stem cell transplantation [16,17]. A number of limitations exist including reduced sensitivity in patients on mold-active therapy, false positive results with use of certain antimicrobials such as piperacillin-tazobactam or those with graft-versus-host disease, and cross-reacting antigens with other fungal organisms (*Fusarium*, *Penicillium*, and *Histoplasma*). (1–3)-beta-D-glucan is another component of many fungal cell walls. Assaying for this antigen is non-specific and can be positive in many invasive fungal infections. The 1-3-beta-D-glucan assay can show false positive results in patients exposed to cellulose filters, those receiving intravenous immunoglobulin or albumin, or

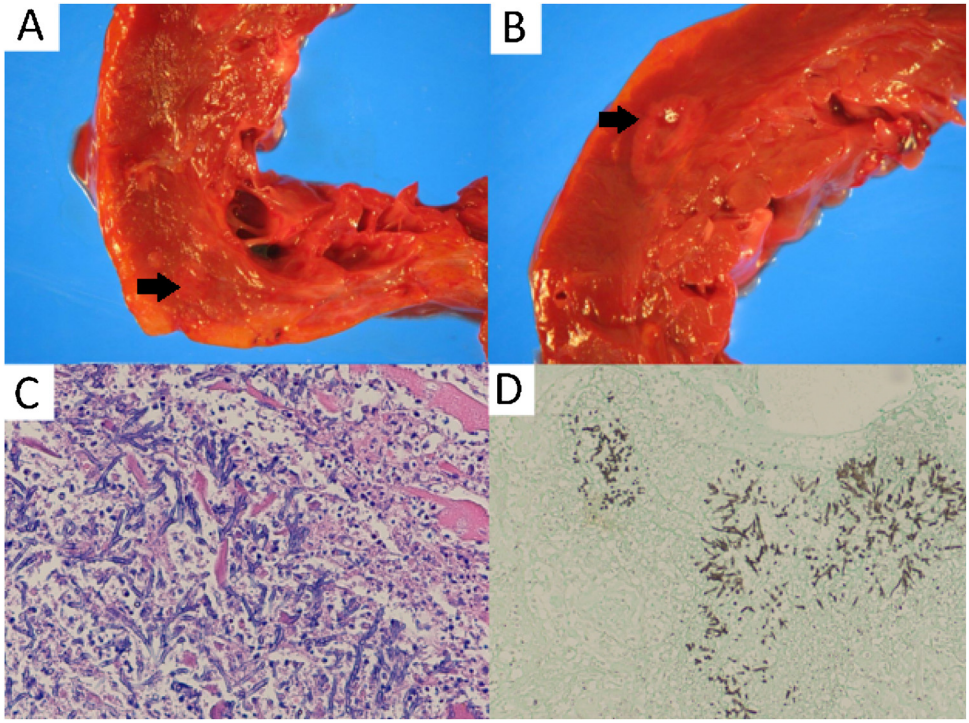

Fig. 1. A, B: Gross photographs of coronal sections of the heart ventricles with myocardial abscesses (pale, soft regions with surrounding erythema indicated by arrows), **C:** Photomicrograph of edge of myocardial abscess (100x magnification) hematoxylin and eosin stain. Hyphae with 45-degree angle branching are seen, with acute inflammation and injured myocytes, **D:** Gomori Methenamine-Silver stain of lung tissue (100x magnification) that highlights fungal organisms with 45-degree angle branching, consistent with Aspergillus.

Table 1
Published case reports of aspergillus myocarditis 1955–2019.

Author	Year published	Number of Cases	Age: mean years (range)	% male / % female	% with positive blood cultures with Aspergillus	Case fatality rate	%pre-mortum diagnosis	Immunocompromising conditions (%)
Welsh et al. [22]	1955	1	18	100 / 0	0	100	0	Primary splenic neutropenia s/p splenectomy, corticosteroids
Fraumeni et al. [23]	1962	1	41	100 / 0	0	100	0	Hematologic malignancy, corticosteroids, chemotherapy
Burke et al. [20]	1970	1	51	100 / 0	100	100	100	corticosteroids, antimicrobials
Castleman et al. [21]	1971	1	33	100 / 0	0	100	0	corticosteroids, antimicrobials
Williams et al. [3]	1973	2	63 (60–66)	100 / 0	0	100	0	Chemotherapy, corticosteroids
Walsh et al. [25]	1980	6	30 (16–61)	0 / 100	0	100	16 (1/6)	Solid organ transplant, hematologic malignancy, corticosteroids
Ross et al. [10]	1985	1	31	100 / 0	0	100	0	Hematologic malignancy
Andersson et al. [11]	1986	3	34 (21–48)	33 / 66	0	100	0	Hematologic malignancy, chemotherapy
Rogers et al. [12]	1990	1	69	100 / 0	0	100	0	corticosteroids, broad-spectrum antimicrobials
Carrel et al. [26]	1991	1	68	100 / 0	0	100	0	corticosteroids
Cishek et al. [9]	1996	1	40	0 / 100	0	100	0%	corticosteroidsand 6-MP
Rouby et al. [24]	1998	1	75	100 / 0	0	100	0	corticosteroids, broad-spectrum antimicrobials
Xie et al. [8]	2005	11	41 (29–62)	100 / 0	0	100	9% (1/11)	AIDS with CD4 T-cells 10-121 cells/uL
Kemdem et al. [4]	2008	1	19	0 / 100	0	100	100%	corticosteroids, hematologic malignancy
Yano et al. [18]	2010	1	74	100 / 0	0	100	0%	None (tobacco use felt to be contributory)
Yoshino et al. [5]	2013	2	79 (76–81)	100 / 0	0	100	0	Hematologic malignancy, broad-spectrum antimicrobials
Dang-Tran et al. [7]	2014	1	68	100 / 0	100	100	100%	Solid-organ transplant, corticosteroids
Kim et al. [19]	2014	1	63	0 / 100	0	0	100	Aplastic anemia
Kupsky et al. [13]	2016	1	18	100 / 0	0	0	100%	Solid-organ transplant
Bullis et al.	2019	1	61	0 / 100	0	100	0	corticosteroids, Rituximab
Total	N/A	39	45 (16–81)	69 / 31	5	95	18	

those with infections with *Pseudomonas aeruginosa* [16]. Newer modalities to detect aspergillosis under study include detection via a monoclonal antibody of a mannoprotein produced only by actively growing *Aspergillus* spp., as well as a breath test for secondary metabolites using thermal-desorption-gas chromatography/mass spectrometry, although the clinical utility of these tests remains to be proven.

A number of treatment options exist for management of invasive aspergillosis including triazoles such as voriconazole, amphotericin B, and echinocandins. Initial monotherapy with voriconazole has been shown in a large randomized, controlled trial to be superior with respect to survival and reduced adverse effects compared to amphotericin B [18]. Treatment duration of 6–12 weeks is the standard, however, this is based on low-quality evidence and a number of factors must be considered including degree of immunosuppression, disease site, and overall clinical trajectory [16]. Following treatment, secondary prophylaxis is warranted with subsequent periods of immunosuppression [17].

Conclusion

The present case highlights the diagnostic challenge of *Aspergillus* myocarditis as well as its fulminant nature and high mortality. Blood cultures are typically negative and isolation from sputum is often of unclear clinical significance. Non-invasive tests including serum galactomannan and (1–3)-beta-D-glucan assays are imperfectly sensitive and specific and a number of factors may cause false-positive results. Our patient's poor outcome demonstrates that improved diagnostics are needed, and physicians caring for immunocompromised hosts must have a high index of suspicion for invasive aspergillosus in all its permutations.

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Conflict of interests

None of the authors report any conflicts of interest.

Authorship verification

All co-authors have seen and agree with the contents of the manuscript and have contributed significantly to the work.

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